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A ROENTGENOGRAPHIC STUDY OF THE SELLA TURCICA IN ABNORMAL CHILDREN*

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This study is based upon the roentgenographic examination of the sella turcica of 64 children suffering from such abnormal conditions as mongolian idiocy, childhood myxedema, thyroid infantilism, hypothyroidism, hypopituitarism, goiter, spastic paraplegia and other gross deviations from the normal.

In May, 1921, the roentgenographic findings as to the sella turcica in 104 normal children were reported. (1) That study was undertaken as an attempt to establish, if possible, normal sellar appearance and formation as a basis for comparison with the changes in abnormals. The conclusions reached were briefly as follows:

1. The shape of the sella turcica in normal children fall in a general way into three groups: A, circular; B, oval, and C, flat or saucer-shaped, with modification in each group.

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2. There is a marked variation for each age, in both the height and the length of the sella for that particular age. The average height and length of the sella shows a comparatively rapid increase in the first two years with a gradual yet irregular increase from then on up to the age of twelve years.

3. There is no relationship between the shape of the sella and the size of the head except in the case of the flat type which was always found in small heads. It does not necessarily follow that all small heads exhibit this type.

4. There is apparently no relationship between the size of the sella and the size of the head.

5. There is apparently no influence of sex on either the appearance or formation of the sella.

Our results in this series of normal children serve as controls in the series herein reported. Although the literature abounds with numerous statements as to the appearance or formation of the sella turcica in various diseases, there have been very few control studies of normal sellas.

This report deals with four problems:

1. Does the shape of the sella turcica differ in abnormal from that in normal children?

2. Are there any characteristic differences in the formation of the sella in various types of abnormal children?

3. Is there a difference in size of the sella in normal and abnormal children?

4. Has the appearance, formation or size of the sella any clinical or diagnostic significance?

SHAPE OF THE SELLA

Round and oval shaped sellas are found in equal proportions as shown in table 1. In our normal series (table 3) we found that the circular or round sella was more frequently seen. Camp (2), who used our classification in a study of 1,000 sellas, mostly of adults, also found that the circular and oval predominated, but in a different ratio than ours, namely: circular, 22.5 per cent; oval, 67 per cent; flat, 15 per cent. This comparative study of the four series demonstrates that there is little difference in the occurrence of the three groups in normal and abnormal individuals. Both the circular and oval pre-

dominate and the flat shape occurs the least frequently of all. No one shape predominated in any individual disease.

FORMATION OF THE SELLA

To appreciate properly the formation of the sella turcica as depicted on an x-ray film, it is necessary to visualize the anatomical relations. It exists as a depression in the superior surface of the body of the sphenoid, limited anteriorly by the middle clinoid processes and posteriorly by the dorsum sellae, which carries the posterior clinoid process on either side of its tip. The middle clinoids are directly lateral and posterior to

TABLE 1

Classification as to Shape

DISEASE	GROUP A (CIRCULAR)	GROUP B (OVAL)	GROUP C (FLAT)
Mongolian idiocy	8	5	3
Childhood myxedema	5	3	3
Hypothyroidism	3	4	0
Thyroid infantilism	0	2	1
Goitre	2	0	0
Hypopituitarism—			
Obesity in female	0	1	0
Froelich syndrome	1	1	1
With hypothyroidism	0	1	0
Microcephalic idiocy	2	0	0
Hydrocephalic idiocy	1	2	1
Behavior disorder	2	1	0
Spastic paraplegia with mental delinquency	1	4	0
Epilepsy	1	0	0
Moron	0	3	0
Muscular dystrophy with mental delinquency	1	0	0
Congenital idiocy	1	0	0
	28—43%	27—42%	9—15%

the olivary eminence. The sella is covered by an extension of the tentorium cerebelli which is attached to the middle and posterior clinoid processes. All of the pituitary body with the exception of the base of the infundibulum lies below this tentorial extension. The anterior clinoid processes are formed by the mesial ends of the posterior border of the lesser wings of the sphenoid; they are located at a considerable distance lateral to and above the diaphragma sellae and hence the olivary eminence and the optic chiasmal groove are extrasellar. The difference then in configuration of the sella caused by the difference in position of the anterior clinoid processes and variations in height of the olivary eminence can mean absolutely nothing referable to the pituitary body.

Timme (3) in 1921 reported that "in 23 out of 24 cases of mongolian idiocy, radiographs of the skull showed a peculiar change from the normal in the anterior fossa pituitaria. This change consisted in an excavation under the anterior clinoid

TABLE 2

Classification as to Presence of Excavation

DISEASE	UNCOVERED	COVERED	NOT SHOWING
Mongolian idiocy	6	6	3
Childhood myxedema	3	5	2
Hypothyroidism	2	3	0
Thyroid infantilism	2	1	0
Goitre	0	2	0
Hypopituitarism—			
Obesity in female	1	0	0
Froelich syndrome	0	1	2
With hypothyroidism	0	1	0
Microcephalic idiocy	1	0	1
Hydrocephalic idiocy	1	2	1
Behavior disorder	1	2	0
Spastic paraplegia with mental delinquency	2	2	1
Epilepsy	1	0	0
Moron	0	2	1
Muscular dustrophy with mental delinquency	0	1	0
Congenital idiocy	0	1	0
	20—33%	29—48%	11—18%

TABLE 3

Comparisons Between Sellas of Normal and Abnormal Children

A—PRESENCE OF EXCAVATION

	NORMAL	ABNORMAL
Present—Covered	29 sellas—38%	29 sellas—48%
Present—Uncovered	30 sellas—39%	20 sellas—33%
Not present	17 sellas—22%	11 sellas—18%
Present—Covered and uncovered	77%	81%

Irrespective of mental condition of child, the excavation was demonstrable either covered or uncovered in 79% of all sellas studied.

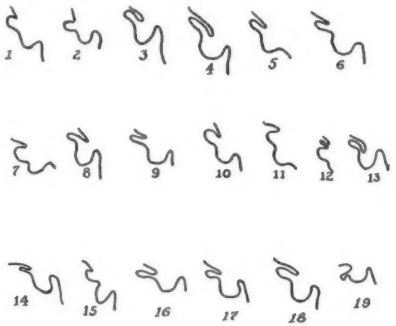
B—SHAPE OF SELLA

	NORMAL (First Series)	ABNORMAL
Group A (Circular)	66%	43%
Group B (Oval)	24%	42%
Group C (Flat)	10%	15%

processes and presumably under the olivary process and optic groove and the excavation itself communicated directly with the anterior portion of the fossa itself." As corroborative evidence that these findings were abnormal, he offered for com-

parison a sella from a normal Chinese girl 13 years of age which did not present this excavation. He further stated that "the excavation is seen occasionally in persons who have not Mongolian characteristics, but who have isolated symptoms and signs due to anterior lobe disturbance, namely, growth and genital developmental abnormalities."

In our first paper we stated that in normal children we found that "in some instances the anterior clinoids are raised above the level of the middle clinoids and are very long. In these latter cases a slit is seen running anteriorly from above the middle clinoid processes under the anterior clinoids. This slit is no way a part of the sella."

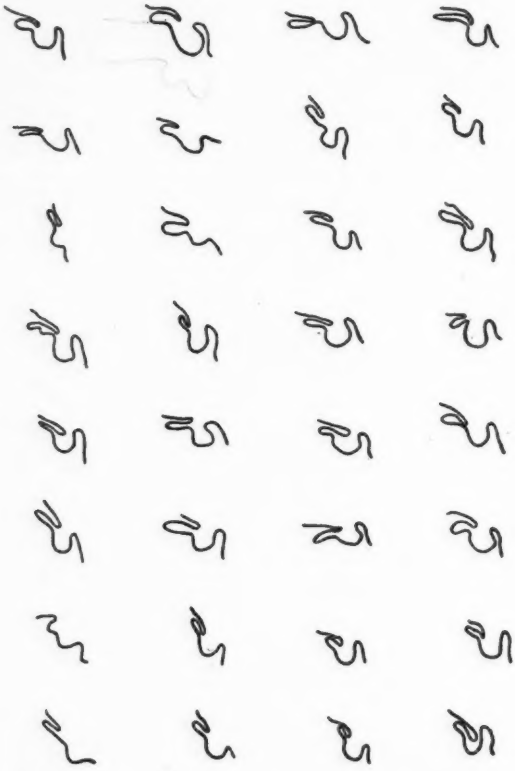


SELLA IN ABNORMAL CHILDREN
SHOWING UNCOVERED EXCAVATION

FIGURE 1

This excavation is made up below of the optic chiasmal groove anteriorly and the olivary eminence posteriorly; above by the posterior portion of the inferior surfaces of the lesser wings of the sphenoids, the tips of which are the anterior clinoid processes. In this paper we have designated the excavation as being either uncovered or covered. By an uncovered excavation is meant one in which the lesser wings of the sphenoid are high enough to permit a visualization of the slit in the lateral view. This is the type described by Timme and by ourselves in the

first paper. In addition to this formation, we now find that in a large number of cases, both normal and abnormal, the slit is easily made out but it is covered by the lesser wings of the sphenoid as shown in figures 3 and 4. This we have termed a covered excavation or slit.



SELLA IN NORMAL CHILDREN
SHOWING UNCOVERED EXCAVATION

FIGURE 2

Tables 2 and 3 show the incidence of each type of excavation in each individual disease studied and also in normal children. The uncovered excavation was found in 33 per cent of the sellas of abnormal children and in 39 per cent of the normal.

The covered excavation was present in 48 per cent of the abnormal and in 38 per cent of the normal children. The excavation was present, either covered or uncovered, in 79 per cent of all cases studied, irrespective of the mentality of the child.

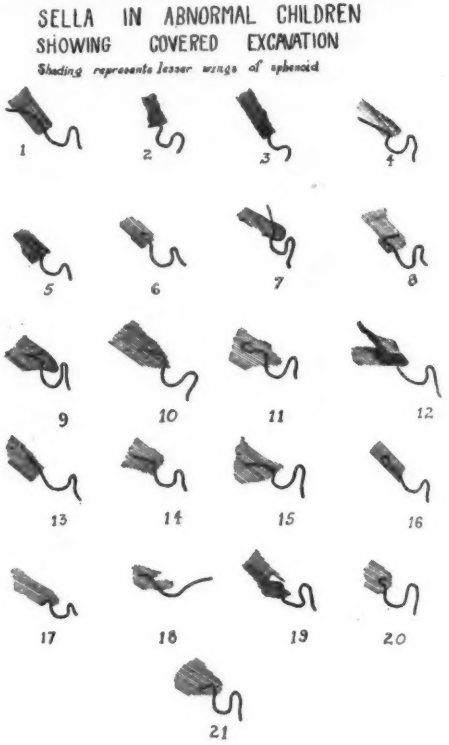


FIGURE 3

Erratum—Figure 3, Number 15. Muscular dystrophy with mental delinquency instead of microcephalic idiocy.

Even a casual examination of figure 1 will demonstrate that it is impossible to differentiate by means of this excavation between the sellas of the various diseases: Mongolian idiocy (Nos. 3, 4, 5, 6), childhood myxedema (No. 8), hypothyroidism (Nos. 9, 10), epilepsy (No. 13), hydrocephalic idiocy (No. 16),

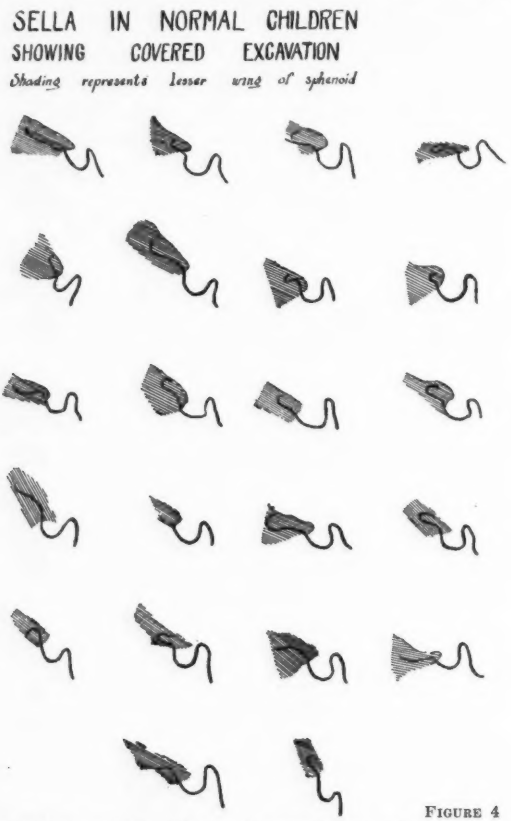


FIGURE 4

behavior disorder (No. 17) and spastic paraplegia with mental delinquency (No. 18).

Similarly, every variation and type of the abnormal group is duplicated in the normal (Fig. 2).

Comparison of the covered excavations found in the abnormal (Fig. 3) and the normal groups (Fig. 4) shows that it is

also impossible to differentiate by means of the excavation between normal and abnormal.

A smaller group is shown in figure 5, in which the excavations are not seen. This type, though it is the most infrequent,

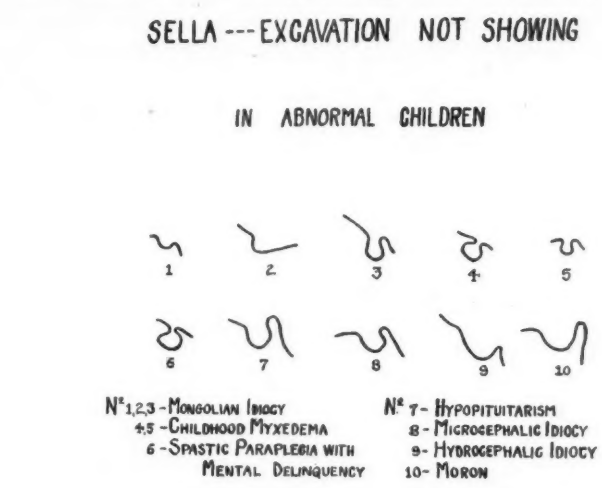


FIGURE 5

is generally accepted as the normal. Here also every variation of formation and contour appearing in the abnormal children is duplicated in the normal.

The characteristics of the anterior and posterior clinoid

TABLE 4

*Size of Sella Turcica in Various Diseases Compared with That in Normal Children**

AGE	SIZE	NORMAL
MONGOLIAN IDIOCY		
14 mos.	8x4 cm.	7x5 cm.
7 yrs.	9x8	9x8
10 mos.	5x4	8.5x6
2 yrs.	10x3	8x6
12 mos.	7x4	7x5
12 mos.	7x4	7x5
2 yrs.	10x7	8x6
3 yrs.	9x6	7x6
12 mos.	1x6	7x5
10 yrs.	5x4	8.5x7.5
2 yrs.	6x6	8x6
9 yrs.	10x5	8.5x7
7 yrs.	11x7	9x8
12 mos.	10x6	7x5
5 yrs.	6x5	8x7
THYROID INFANTILISM		
6 yrs.	9x6	8x6.5
3 yrs.	7x4	7x6
3 yrs	4x3	7x6
MICROCEPHALIC IDIOCY		
15 mos.	8x5	7.5x6
8 yrs.	7x6	8x7
HYDROCEPHALIC IDIOCY		
5 yrs.	11x5	8x7
21 mos.	9x6	8x6
8 yrs.	8x7	8x7
2 yrs.	12x8	8x6
SPASTIC PARAPLEGIA WITH MENTAL DELINQUENCY		
2 yrs.	8x4	8x6
2 yrs.	7x4	8x6
13 mos.	7x5	7x5
2 yrs.	1x5	8x6
4 yrs.	5x5	7.5x6.5
MUSCULAR DYSTROPHY WITH MENTAL DELINQUENCY		
7 yrs.	7x7	7.5x7

AGE	SIZE	NORMAL
CHILDHOOD MYXEDEMA		
6 mos.	9x3 cm.	8.5x6 cm.
12 mos.	9x5	7x5
3 yrs.	8x4	7x6
3 yrs.	6x5	7x6
3 yrs.	7x2	7x6
6 mos.	7x3	8.5x6
5 yrs.	7x7	8x7
HYPOTHYROIDISM		
4 yrs.	10x4	7.5x6.5
28 mos.	8x5	8x6
4 yrs.	9x6	7.5x6.5
2 yrs.	9x4	8x6
3 yrs.	8x7	7x6
7 yrs.	6x7	9x8
7 yrs.	7x9	9x8
GOITRE		
7 yrs.	7x9	9x8
8 yrs.	8x8	8x7
HYPOPITUITARISM		
13 yrs.	10x6	10x8
13 yrs.	12x5	10x8
12 yrs.	10x6	7.5x6
12 yrs.	8x9	7.5x6
BEHAVIOR DISORDER		
6 yrs.	10x7	7x6.5
6 yrs.	9x7	7x6.5
8 yrs.	8x7	8x7
EPILEPSY		
6 yrs.	8x8	7x6.5
MORON		
10 yrs.	11x7	8.5x7.5
8 yrs.	10x8	8x7
CONGENITAL IDIOCY		
4 yrs.	7x5	7.5x6.5

*Normal figures taken from averages in first paper.

processes show the same variations in size, shape and development in the sellas of abnormal children as were found in those of normal children. Only one sella showed bone changes and that was in a hydrocephalic idiot who presented a type C sella with poorly developed dorsum sellae with probable absorption of the anterior clinoid processes since they were not seen. No slit was demonstrable due to the absence of the anterior clinoids.

SIZE OF THE SELLA

The variations in the normal series were so great that it was difficult to arrive at an average for any particular age. The same variations in size are noted in this series, and it is therefore more difficult to state whether the changes in size are due to the disease or whether they represent the same normal variations. It seems, however, that the type of disease has apparently no influence on the size of the sella, for the differences are not constant enough for any one disease to be of value. For instance, in three cases of infantilism with, of course, small heads the sella of only one was smaller than the average for that age. In large heads such as met with in hydrocephalic idiocy, two showed sellas larger than that generally seen at the age of the child. One of these was in the largest head in the series, the largest sella and the only one showing bone absorption. As evidence that the size of the sella is per se of not much importance, it may be stated that sellas of almost the same size were found in a case of Froelich syndrome with normal mentality and in a moron, both with normal sized heads. The various types of diminished thyroid activity did not present any essential difference in size from those with goiter. Mongolian idiocy and hypopituitarism showed some of the largest sellas encountered in the series but with not enough regularity to make it of etiological or diagnostic importance.

SUMMARY

Studies were made of the contours of the sella turcica in 64 abnormal children. The findings were compared with those of 104 normal children. It was found that the shape of the sella does not differ significantly in normal and abnormal children. The type of disorder is not correlated with the shape of the

sella. Round and oval shapes predominate both in abnormal and normal children and flat sellas are the least frequent.

The formation of the sella does not differ in abnormal children from that in normal children. There is no formation characteristic of any individual disease. The excavation that has been described in Mongolian idiots is extrasellar. It may be uncovered or covered by the lesser wings of the sphenoid. It is a normal foundation found with the same frequency in all children and is not characteristic of any known disorder.

The size of the sella is not influenced by any of the diseases studied. As in the normal series, there was found no relationship between the size of the sella and the size of the head nor between the shape of the sella and the size of the head.

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STUDIES ON VIGOR. IV. THE EFFECT OF TESTICLE GRAFTS ON SPONTANEOUS ACTIVITY*

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In a previous research it was shown that castration results in a striking diminution in spontaneous activity. Various studies have been made with view of re-energizing the castrated animals. It is the purpose of this paper to report the negative results obtained with testicle grafts.

Of late years a considerable number of reports have appeared on the efficacy or the lack of efficacy of testicle grafting in the treatment of a variety of conditions. The older literature and some of the more recent contributions have been discussed in several general works such as Biedl (1913), Lespinasse (1922), Lipschütz (1924), Thorek (1924-a) and Wheelon (1922).

AUTOGRAFTS

In general three types of grafts have been utilized, namely autografts, which of course amount merely to a transposition of the animal's own glands to an abnormal situs; homografts, between like species; and heterografts, from one species to another.

The first definitely successful testicle transplantation on record, namely, that of Berthold (1849), was of the autograft type. Cocks were castrated, the glands cut into bits and these sprinkled over the peritoneal surface. This procedure resulted in normal sexual development of what would otherwise have been capons.

Loeb (1918) included the testes in a series of organs that were grafted in guinea pigs with a view particularly to studying the resulting histological changes. He found that the content of the seminiferous tubules was transformed to a hyalin material, which later was in part substituted by cells that resembled mesenchymal epithelium. No data on the behavior of the animals were cited.

Ocaranza (1922) made similar studies in guinea pigs. He noted an almost complete disappearance of the interstitial cells and degeneration of the seminiferous tissue within a period of a month. He found that castrated animals carrying such grafts retained their sexual instincts, but he was unable to cause any apparent change in the maternal instincts of ovary-bearing females.

Sechi (1923) made similar grafts in rabbits from three months to three years old. The grafts when examined histologically from twelve days to three months later were found to be mostly degenerated. No specific conclusions were reached.

Lundy (1925) has recently repeated this work in rats with a

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view particularly to determining the viability of glands kept for a time outside the body. In case of Primates different authors have reported that successful results are obtainable with material collected as long as twenty-four hours after death and kept refrigerated as long as seventy-two hours. Even with the utmost care when slices of testicle or whole organs were transplanted into the scrotum, which seems to be the most favorable size, Lundy found that no grafts persisted that had been kept longer than twenty-four hours, though successful results were easily secured with fresher material.

HOMOGRAFTS IN ANIMALS

Ocaranza, Loeb, Sechi and Lundy included homografts as well as autografts in their experiments reported in the preceding paragraphs. The results apparently were quite similar in both types.

Wheelon and Shipley (1916) made a study of the effect of testicle grafting on the irritability in the sympathetic nervous system in thirteen dogs. It was found that this irritability, as estimated from the vasomotor reaction to injected nicotin, was depressed fifty per cent by castration. Following the implantation of testicle grafts the vasomotor irritability within periods of seven to twenty-two days was restored on an average of seventy per cent of the normal.

Lipschütz (1917) reported on the effects of grafting testicle into female guinea pigs previously spayed. Steinach had previously reported that this operation results in psychological masculinization of the recipients. Lipschütz considered primarily the somatic changes. He found that the clitoris showed considerable hypertrophy, resulting in a penis-like structure. The control spayed animals showed no such change.

Moore (1919) reported the results of a careful study of homografting from male to spayed female rats. Usually litter mates were used as donors and recipients. The grafts were removed from the males and immediately placed beneath the fascia of the abdominal muscles on either side of the mid-ventral line of the females, which were spayed at this same operation. A very marked degree of masculinization was shown. The animals carried out sham copulation with rutting females in a surprisingly realistic way. Moore states that no such behavior had ever been seen by him in non-grafted, spayed females. Later, upon examining the site of the graft histologically it was found that the seminiferous tubules had become more or less scattered under the fascia and among the muscle fibers. The tissue was largely degenerated, the tubules containing an irregular lining of large cells, interpreted by the author as Sertoli cells. The lumens were mostly filled with a reticular substance. Numerous cells were seen among the tubules which were interpreted as "interstitial cells."

Harms (1920) reported the case of a senile guinea pig that received a testicle graft from his six weeks' old son. His potency was restored for a period of a half year.

Moore (1921) reported the results of testicle grafting into eighteen young spayed female guinea pigs. The grafts in the two successful cases persisted seven and nine months, respectively. Marked psychic masculinization and enlargement of the clitoris was noted. The testicular tissue seems to have been preserved unusually well. Histologically the tubules showed a "typical condition" except that spermatozoa were absent.

Bolognesi (1921) reported that after removal of a segment of the vas deferens and the epididymis atrophy of the seminiferous tubules and hypertrophy of the interstitial cells of the testis resulted.

The gland thus modified when transferred to another animal produced no detectable effect.

Romeis (1921) removed one testis and ligated the vas deferens of the other in a sterile and impotent senile rat. Later two halves of a testis from a young rat were implanted. The recipient became more lively, its appetite improved and it took on weight. Eleven days after the operation it attempted to copulate, but later became again indifferent to females.

Voronoff (1922) reported the results of four years' work, including 120 cases of testicle grafting in men and higher animals. It is claimed that striking results were frequently obtained both in the sex sphere and as regards such conditions as strength, initiative and feeling of bodily well being. In various instances, however, negative results were secured.

Wilhelm (1922) reported the case of a seven year old castrated dog into which were grafted the testes from a sexually potent dog one and a half years old. There was a considerable revival of the sexual function. Histological study showed some tendency toward a restoration of the ganglion cells from their previous senile stage.

Zawadowsky (1922) succeeded in getting a "take" in only one of six cases in which testicle grafts were placed in normal hens. In ovariectomized hens more successful results were secured. In two cases the grafts "took" even though the ovary had in the meanwhile more or less regenerated. In the successful cases hypertrophy of the comb took place though this structure did not become as erectile as in the normal cock.

Wilhelm (1923) continued his studies in aged dogs, adding three more cases. A subcutaneous implant is stated to have resulted in temporary improvement in vitality. After remission two years later an intratesticular transplant was made with no results. In a second case an intramuscular and intratesticular implantation was made. Although the animal for a month before on good diet had failed to gain in weight, after the operation it increased from six to eleven and a half kilograms. There was a return of potency and marked aggressiveness developed. The coat improved and an arcus senilis partially cleared up. The improvement lasted for three and a half months, after which regression began. In another animal an intramuscular transplant resulted in return of potency and improvement in general bodily condition, but two and a half months later a sudden regression took place.

Harms (1924) transplanted the testes of a three to five months old dog into an old animal. The senile testes were reported to have been restored to full functional state.

Kustria (1924) transplanted subcutaneously the testes of a one year old cat to a twelve year old. Improvement in appetite, liveliness, hair coat and weight were noted. Nineteen days after the operation six new teeth appeared and later four others errupted. These were retained until the death of the animal seven months later.

Pézard, Sand and Caridroit (1924) reported a successful testicle graft in a castrated female fowl. A large male-like comb developed. Necropsy showed the presence of both normal ovary and active sperm-forming testis. In a castrated male the re-establishment of secondary sex characteristics following a graft was reported.

Lundy (1925) failed in case of homografts as in autografts in rats to obtain any takes when the transplantation was made later than twenty-four hours after removal from the body of the donor.

HOMOGRAFTS IN MEN

Apparently the first reported case of grafting in man is that of Hammond and Sutton (1912). A testis was transplanted in toto with

blood vessel anastomosis. The graft ultimately became markedly atrophic. Since the subject had one sound testicle results cannot be evaluated.

The first case reported with definite benefit is that of Lespinasse (1913). Among the fibers of the right rectus muscle of a castrated man of thirty-eight were introduced slice grafts about 1 mm. in thickness from a fresh human testis. A slice was placed also in the scrotum. The subject became markedly erotized within four days. The effect was stated to be still strongly in evidence two years later.

Morris (1916) reported an especially interesting case of a man of twenty-seven with a high degree of testicular atrophy which followed an attack of mumps at the age of thirteen. Three slice grafts about 3 mm. thick from a man of fifty-four were placed under the right and left rectus abdominis muscles and in the scrotum. While placing this latter graft it was noted that barely a trace of the original testis was to be seen. The graft gradually disappeared, but the atrophic testis began to grow, reaching one-third normal size. At a second operation another intratesticular graft was made, giving opportunity for a second examination of the testis. It now had a normal appearance. The subject experienced a considerable degree of masculinization.

Lydston (1916) reported four cases, but in two no significant data as to results were included. His first subject, a young man of twenty-two, suffered from dementia precox. An intrascrotal implantation was made of the whole testis of a man dead of cocain poisoning. Considerable symptomatic improvement followed, but the well known changeability in dementia precox renders precarious any judgment as to the part played by the operation. Seven months after the implantation the gland was firm and about one-half its original size. Another man suffered from post-traumatic testicular atrophy. His bodily configuration verged toward the feminine type and his beard was sparse. He was sexually impotent. The testes of a fourteen year old boy dead of trauma were obtained six hours after death and kept on ice in saline solution for thirty-three hours, then implanted in the scrotum. Marked increase in bodily vigor with restoration of potency to rather more than normal was claimed. Seven months after the operation the glands were moderately atrophied. The subject had lost twenty pounds in weight ("flabby fat"). Fifteen months later the gland still showed moderate atrophy, but sex activity was reported as still vigorous. Two and a half years after the operation (1918) the subject was keeping up vigorous athletic activity. His weight was forty pounds less than before the operation. His sex power was reported as normal. The grafts were firm and "somewhat smaller than those of a boy of thirteen." The case was added of a boy of nineteen with very marked testicle atrophy following orchitis. He was distinctly feminine in general bodily appearance and the sparse hair growth was suggestive of that of a young girl. The testes of a boy of fifteen dead of carbon monoxid poisoning were implanted. These had been obtained twenty-four hours post-mortem and kept refrigerated thirty-two hours. Sixteen months later the glands were soft and about the size of those of a twelve to fourteen year old boy. The virility of the subject after the operation was reported as markedly augmented. In 1921 two other cases were added. A man of thirty-four had rather feminine bodily characteristics and infantile genitalia. He was inefficient mentally, physically, and sexually. Following a scrotal implantation of a testis of an eighteen year old boy the nutrition improved, there was considerable growth of pubic and axillary hair and enlargement of the genitalia. The sex activities became vigorous. A man of

thirty-six had lost both testes at the age of thirty from tuberculosis. His beard had largely disappeared and he had developed a fat, somewhat feminine body type. His sex power and mental and physical efficiency were depressed. A double testicle implantation was made with disappointing results. Ten months later, after a single gland graft, he lost twenty-six pounds and apparently improved sexually and nervously.

Mariotti (1919) reported a case of testicular deficiency in a man of twenty-one. Part of a healthy gland was grafted into his flank. Temporary improvement confined to the genital sphere followed.

Kreuter (1919) reported the case of a man generally "run down" from tuberculosis. Following normal testis implantation his sexual activity was stated to be considerably augmented.

Stanley and Kelker (1920) reported eleven cases of homografting. In some instances the grafts were denuded of parietal tunica and implanted in either the scrotal bed or upon the atrophic testes of the recipients. In one instance both sites were used. The authors derived the impression that better results were secured by the second method. In general, a single testis seemed to give as good results as two. Three cases were cited in some detail. A man of twenty-five was dull and inactive. He received a double graft from a man of twenty-seven. He became more energetic and reported greater sex activity. In a man of fifty testicle atrophy had resulted from orchitis. He showed rather marked debility. A graft was made from a man of twenty-seven. Five days later an increase of sex activity was reported. At the end of eight and a half months the graft was reduced to the size of a cherry. It was removed for histological examination and found to be entirely necrotic. In a man of fifty-four testicular atrophy had resulted from mumps. He showed sexual debility and mental languor. He received a double graft from a man of twenty-six. There was awakening of sexual activity on the fourth day and in a month this had become vigorous. In vitality and aggressiveness he was markedly improved. His vision was found by an oculist to be fifty per cent better than that indicated by a prescription for glasses that he had been given several years before. A sickly, peevish man of seventy-two, unmarried, had always shown depression of sex tendencies. He received a double graft from a nineteen year old boy. He claimed to be considerably erotized and was markedly improved in general vigor and spirits. His voice became deeper and stronger.

Lichtenstern (1920) claims successful results in castrated eunuchoid subjects. His technic was to implant fresh testis on the scarified muscle inside the rectus sheath in the inguinal region. In castrates such deficiencies as bodily and nervous depression, loss of hair and loss of libido are stated to have been fully restored. In cases of homosexuality both the psychological and somatic deviations were corrected. In the eunuchoids there resulted new growth of body hair, deepening of the voice and enlargement of the genitalia. Sexual activity was stimulated and even the formation of spermatozoa in the subject's own testes followed. Lichtenstern's observations were continued in some cases as long as five years. In 1921 the results obtained in twenty-two cases since 1915 were summarized. In general they were stated to be excellent, with continuation of the sexual functions for years.

Stabel (1921), on the other hand, performed testis implantations in six cases of homosexuality with uniformly negative results.

Mühsam (1920-21) reported that testicle grafts in three subjects, a castrate, a bisexual and a homosexual man, gave splendid results. In 1922 he summarized the results of six transplantations in five

patients. A castrated man received a graft; seven months later libido had returned. After eleven months he married and, it is stated, had normal intercourse. A bisexual subject of twenty soon after an implantation developed heterosexual inclinations. A homosexual subject received grafts upon two occasions. These were followed by brief heterosexual periods, but no permanent results. From another homosexual subject one testis was removed and another implanted. He showed normal sex tendencies four months later. After implantation of a graft in a castrated man of thirty years the only result was a slight sex stimulation for a short period.

McKenna (1921) recorded the case of a man, aged twenty-six, who had been castrated for testicular tuberculosis. An ectopic testis secured from another man was implanted. Improvement in general health, strength and potency began within a few days and continued up to the time of the report eight months later.

Förster (1921) transferred a testis of a man of twenty to a man of fifty-five showing precocious senility. The results were negative. At autopsy three months later the graft was recovered and found to be completely necrotic.

Enderlen (1921) reported two cases of homoplastic and two of heteroplastic grafts in the abdominal musculature. A few weeks later microscopic examination showed complete necrosis of the parenchyma. It was concluded that such grafts are futile.

Voronoff (1922) claimed a considerable number of successful results from homografts in man.

Gregory (1922) split the testis of a normal man and implanted it between the abdominal muscles of a man of sixty-eight, who showed marked fatigability and lack of libido. It is stated that his feeling of exhaustion was lost and the sex feeling of a man of forty was regained.

Kreuter (1922-a), who had formerly favored testicle grafting, reported that his experience did not bear out the favorable claims for the method. He reported the cases of a homosexual man in whom one testis was replaced by that of a normal subject and of a castrate who received a gland of a homosexual subject. No significant results were secured. This author had opportunity (1922-b) to examine two human grafts three weeks and two years, respectively, after implantation. He noted necrosis of the spermatogenic elements, and extreme reduction in the interstitial cells of the former and complete absorption in the latter.

Nakada (1922) reported the case of a man suffering from tubucular epididymitis who received a normal gland graft. For a few months there was marked improvement in the sexual condition and the neurasthenia from which he suffered, but the implant became atrophic and he relapsed to his previous condition.

Pfeifer (1922) recorded the case of a man of thirty-three who from the age of twenty-one to thirty had shown no psychosexual abnormality. He then developed a homosexual trend. Examination showed pubic crines somewhat resembling the female distribution. At an operation for hernia a piece of testicle was engrafted without the patient's knowledge. A few weeks later increased pubic hair growth was noted and the subject, it is stated, had again become normally heterosexual.

Sand (1923) made transplants in two homosexual subjects. A year later no indubitable results had been obtained. The implanted material seemed to have been resorbed.

Brandt and Lieschied (1923) reported four human cases. In two young men and one man of fifty-two the results were almost or completely negative. In one man of twenty-nine transient improve-

ment was seen. In seven animal experiments the results were negative. These authors concluded that testicle grafting is merely a type of psychotherapy.

HETEROGRAFTS IN ANIMALS

Aside from human cases, apparently few experiments have been made on grafting testes from one species to another. The only report encountered in this study is that of Thorek (1924-b), who states that six weeks after implantation of a cryptorchid human testis he obtained marked erotization of a Macacus nemestrinus that had been castrated about a year before. The evidence in this case was, of course, objective. He reported also successful results from the interchange of testes among different species of higher apes.

HETEROGRAFTS IN MEN

Stanley and Kelker (1920) reported five instances of slice grafting of ram's testis into human subjects with some improvement. Few details on this particular point were included in their report.

Falcone (1920) used ram testis for implantation experiments on four men aged fifty-three, sixty-three, sixty-nine and seventy-four years, respectively. He reported that the general health and the sexual condition in these subjects were much improved and in two cases exaggerated sexual excitability resulted. The patients were not told, it is stated, what results were to be expected from the operation. It was noted that the size of the testes of the subjects increased.

Lichtenstern (1921) recorded excellent results in a series of cases, in one of which ram's testicle was used.

Hunt (1922) also used slice grafts from the ram in three cases. In a man of sixty who was impotent several months of improvement seemed to follow. Some degree of potency was restored, the appetite was improved and there was fifteen pounds gain in weight. At the end of the year, however, the patient decided that the benefits had been merely imaginary. General debility and impotence in a sailor of sixty-five were reported as greatly benefited, though most of the graft sloughed out within a period of three weeks. It is stated that his hair, which had become gray, was largely restored to its original brown color. In a man of forty-eight a similar graft resulted in return of potency in three weeks.

Voronoff's (1922) experiments which included heterografts have been previously referred to. He stated that monkey grafts into the testes of the recipient gave good results. He prefers, however, the peritoneum or tunica vaginalis because the transudation of plasma in these sites supplies nourishment to the graft while it is being vascularized. Subcutaneous or muscular grafts, in his experience, undergo necrosis and last only a few months.

The most extensive study of heterografts in man have been reported by Stanley (1922). He made a thousand implantations, mostly heterografts, in 656 human subjects. To some extent slices were used, but for the most part the testicular substance was introduced subcutaneously by means of a syringe and large bore hypodermic needle. In Stanley's opinion the latter technic is quite as efficacious and can be carried out with ease and with only minor discomfort to the subject. His observations have the defect of lack of quantitative criteria and of adequate controls except as each subject served as a control on himself. Since the experiments were made largely in a penitentiary in which environmental factors presumably were unusually constant, comparison in the individual subjects before and after the implantation were more significant than would ordinarily be the case. Following the implantation many sub-

jects showed striking objective improvement in such conditions as asthenia, acne, asthma and senile debility. There often seemed to be a significant degree of improvement in other conditions such as rheumatism, neurasthenia and even poor vision.

Retterer and Voronoff (1923) reported the transfer of the testes of a five or six year old ape into two men. One was run down, obese and impotent. Three months later he showed a reduction of seven kilograms in weight and improvement in strength and memory. His genital function was completely restored. In a second case the results were negative.

Thorek (1924-b) summarized the results of ninety-seven transplants in men observed over a four year period. These include fifty-seven heterotransplants, the glands being obtained from various Primates. In sixty-nine cases designated as senility marked improvement was reported in forty-four. Beneficial results were claimed also in eunuchism, neurasthenia and dementia precox. In the total series fifty-two per cent showed either complete symptomatic recovery or marked improvement. The remainder showed slight or no improvement. The author used a special technic in that the tunica was fenestrated before implantation of the gland. Thorek regards freedom from pressure on the graft essential. The two most favorable sites in his experience are the supraperitoneal space in the region of the deep epigastric vessels or the retrorenal fossa. Successful results were claimed with tissues refrigerated as long as seventy-two hours.

Lipschütz and Krause (1924) reported the case of a man of thirty-nine who at twenty-four had sustained severe trauma of the testes. A fourth of a gland from a young goat was implanted in the sheath of his rectus abdominis. Within two days strong libido and erections were restored and shortly thereafter potentia coeundi. The beneficial effect persisted for several months, though the graft was resorbed.

Lisser (1924) has recently reported a striking case of improvement in a eunuchoid, a man of thirty-one whose testes had atrophied as a result of trauma eleven years previously. He was mentally and physically sluggish. His nails showed onychauxis. A fresh slice graft from the ram was made in the abdominal wall. This was followed by a gain of five pounds in weight, marked increase in the size of the patient's testicular remains and a sense of well being and increased strength. He was able to remain employed with considerably greater success after the treatment. The nails became somewhat smoother during this time. Twenty-one months later, after a nervous breakdown, about 4 cc. of ram's testicle substance was administered by the Stanley technic in the abdominal wall. The patient gained seven pounds in the first week succeeding. He gained in strength and returned to work. Treatment was repeated three times in the next year, the material being gradually absorbed in the interim. At the end of this time the finger nails had become entirely normal.

DISCUSSION

Technic. There is no uniformity of testimony as to the best method of making testicle grafts. Sand (1921) after somewhat extensive experience has stated that results depend very largely on technic. The place of the graft or even the consanguinity of the donor and recipient he regards as of lesser importance, but emphasizes the necessity of having the implant

surrounded by vascular tissue. Voronoff has reported good results when the grafts were placed in the recipient's testes, but he prefers to place them beneath the peritoneum or in the tunica vaginalis because the abundant lymph in these situations assures sufficient nourishment to maintain the graft until vascularization can occur. In his experience subcutaneous or intramuscular grafts are soon resorbed. In this opinion he is sustained by a considerable number of investigators. Moore, however, has reported microscopic evidence of long persistence of implanted tissue even within the rectus abdominis muscle. Many observers have reported temporary benefits from intramuscular implants. Lydston claimed good results from intrascrotal implants of whole glands. Thorek has used a similar technic except that the tunica of the gland was fenestrated by way of facilitating vascularization. Stanley has reported numerous experiments using scrotal grafts, the glands first being more or less denuded of tunica, as well as slice grafts upon the recipient's own testes or intramuscularly. More recently he has adapted a method of placing the testis material free from tunica in a large syringe and implanting it through a wide bore needle subcutaneously. He believes as satisfactory results are obtained by this method and with much greater ease, though ultimate resorption is to be expected.

In human experiments the problem of freshness of material is important. Lydston claimed successful results with whole glands obtained twenty-four hours after death and kept refrigerated thirty-three hours. Thorek claims that the material can be kept as long as seventy-two hours before implantnig. Lundy, on the other hand, in an investigation directed specifically to this point obtained no "takes" in rats with tissues kept longer than twenty-four hours outside the body. From what is known of gland grafting in general this latter result would be expected. On the basis of general experience, including that in cell culture work, it seems difficult to believe that tissues of higher animals could survive four days of deprivation of nourishment, stasis of excretory products and only such restricted respiration as could be provided by diffusion into relatively large masses. So far as this study has disclosed, Thorek is the only observer who has submitted histological evidence of the persistence of such grafts.

Although some observers have claimed good results from grafts into castrates, and, indeed, in the lower animals have submitted convincing evidence of the efficacy of such grafts, one gains the impression that in man better results are secured when at least rudimentary testes are already present. In various instances following implantation of either human or goat material, both enlargement of the rudimentary glands and such objective changes as growth of hair, rapid gain in weight and changes in the nails have been reported.

Histological Changes in Implants. Several observers have reported careful studies on this topic. Loeb, working with guinea pigs, found that the contents of the tubules became hyalinized and later partly substituted by mesenchyma-like epithelium. Moore (1924) has found a good deal of variability in different cases in man, rat, and guinea pig. Typically, after a period in the recipient the tubules are found well outlined, smaller than normal, and lined with a single layer of Sertoli cells that are often the sole remains of the germinal epithelium. The tubules are widely separated and there is a great abundance of interstitial cells persisting as well as some connective tissue. In more favorable cases, however, a considerably greater degree of persistence of the spermatogenic tissue was noted and even in one case the actual formation of spermatozoa in the graft. Retterer (1919) obtained rather similar results in sheep and goats. In his experiments only the superficial parts of the implant that were freely supplied with lymph survived. A very few of the tubules showed persistence of epithelium to the extent of producing spermatozoid heads, but for the most part the contents of the tubules were transformed into syncytial masses of finely reticulated connective tissue. Kurtzahn studied homo- and auto-grafts introduced either as slices or by the Stanley method into muscle, peritoneum, spleen and liver. The Stanley method gave longer persistence, but in either case the implants ultimately necrosed and were resorbed. Ishiyama (1922) found that in rabbits in all cases the implants underwent necrosis, including both the interstitial tissue and the tubules. The spermatozoa he found materially outlived the other cells.

Persistence of Grafts. A considerable number of observers

have reported complete necrosis and resorption. Ocaranza, for example, found that absorption was almost complete in a month. Morris had opportunity at a second operation to inspect the site of a previous intrascrotal slice graft in man and found that it had disappeared. Förster observed at autopsy a graft placed three months before in a man of fifty-five years. It was completely necrotic. Enderlen in four cases of abdominal muscle implant in man found complete necrosis within a few weeks and concluded that such grafts are futile. Kreuter in homografts in man found in one case necrosis of the spermatogenic tissue and extreme reduction of the interstitial cells in three weeks and in another complete absorption in two years. Lydston reported a whole gland implant about half the original size after seven months. In another case the atrophy was only moderate after two and a half years. In a third the gland seemed to be well preserved sixteen months after implantation, despite the fact that it had been refrigerated for thirty-two hours. Stanley and Kelker in a human case removed what was possibly a similar gland that had become reduced to the size of a cherry. Upon histological examination it was found to be entirely necrotic.

Persistence of Beneficial Effects. It is somewhat difficult to derive a clean-cut impression regarding the persistence of beneficial effects of the grafts in various cases because of the frequent use of indefinite criteria such as increased erotic tendencies, feeling of well being or general strength. On this point Förster saw no results in precocious senility at all. Mühsam reported temporary results in man. Sand found resorption with discontinuance of benefit after a few months. McKenna found that the results were markedly in evidence at the end of eight months. Lipschütz and Krause implanted a fourth of a goat gland beneath the rectus sheath. Though the graft was resorbed the resulting erotization persisted several months. Lydston claimed good results for two and a half years and Lichtenstern and Thorek for at least five years.

Amount of Gland Necessary to Efficacy. Since the implants characteristically undergo a marked degree of necrosis it becomes an important practical problem how much functioning tissue is necessary for efficacy. This problem has been

studied by Pézard in fowls and by Lipschütz, Ottow and Wagner in mice and guinea pigs. Using the length of comb as criterion, Pézard found that a graft, the viable part of which amounted to one-half to one and a half grams, insured normal development. If less than this quantity persisted the comb regressed to the capon condition. Pézard postulates for the testicular hormone an "all-or-none law." Lipschütz found that one per cent of the normal testicular weight was enough to insure normal bodily development in guinea pigs, and the mouse was well masculinized when four per cent of the normal gland weight was present.

Subjective Results of Gland Grafting. Many of the reports can not be satisfactorily evaluated because of the intangibility of criteria employed. Such conditions as general vigor, sense of well being, and sex proclivities can be largely influenced by suggestion alone. Even changes of weight may result indirectly from suggestion. A neurasthenic individual relieved of worry and tension, for instance, may improve in nutrition rather strikingly within a short period. Similarly, loss of weight in a sluggish person suddenly re-energized by suggestion might take place. In this as in all types of endocrine work the long arm of coincidence can never safely be neglected. Nevertheless, a considerable number of observers who presumably are fully cognizant of these difficulties have become convinced that testicle grafting frequently has produced genuine improvement in the condition of their patients, both as regards general debility with resulting feelings of inadequacy and as regards sex depression. Despite the inherent difficulty of dealing with them scientifically, it should not be forgotten that subjective feelings are important factors in human life and are amenable to modification by other methods than suggestion. Falcone definitely attempted to eliminate suggestion by keeping his patients in ignorance of the possible results of the operation. He found that marked erotization followed implanting of ram's testis in such cases.

So far as animals are concerned, erotization can be studied more objectively. Steinach's older reports on masculinization of spayed females are well known. Sand has seen well marked masculine behavior in castrated rats after grafting. Although

Stone (1924) has shown that aberrant sexual behavior occasionally occurs spontaneously, it is so unusual as to offer comparatively little difficulty of interpretation in well conducted experiments. In guinea pigs Moore got well marked masculinization, shown convincingly in the belligerent attitude of subjects toward normal males, with the emission of a characteristic masculine challenging cry. The same observer noted strikingly realistic sham copulation upon the part of masculinized spayed rats. Apparently nothing of the sort has been seen in case of normal females. In the higher apes, studied by Thorek, the resumption of sexual manifestations after months of indifference to the opposite sex could not well be mistaken.

In view of the masculinizing effects in experimental animals a number of investigators have considered the possibility of correcting homosexual aberrations by grafting. The most convincing case encountered is that of Pfeifer, who introduced a piece of human testis during an operation for hernia without the patient's knowledge. It is claimed that transformation to the normal took place. Lichenstern also has reported favorable results. Mühsam reported splendid results in one case, but later reported a relapse. Sand in two cases got no indubitable results; Kreuter in one case no significant results, and Stabel in six cases uniformly negative results. In view of the obscurity of the etiology of the condition the probable value of this treatment would be hard to estimate, even granting perfection of the technique.

Objective Results of Gland Grafts. Steinach laid considerable stress on coarseness of the hair, the size and form of the skeleton and the augmented weight of his masculinized animals. As Moore points out, however, these are difficult to determine with satisfactory objectivity and as distinct from incidental nutritional effects. The greater weight reported might have been due merely to the preceding spaying. Sand, Lipschütz and Moore, however, are agreed that testicle grafts result in hypertrophy of the clitoris well beyond the limits of spontaneous variability. Zawadowsky, as well as Pézard, Sand and Caridroit, noted definite enlargement of the comb in fowls bearing testis grafts. Wilhelm made a study of the nerve cells in senile dogs and the effects of testis grafts on these. He noted a

considerable degree of rejuvenation. He noted a gain in weight from six to eleven and a half kilograms in an old dog that during a month's control observation on an excellent diet had failed to gain in weight. Kustria reported the eruption of ten new teeth in a twelve year old cat. Thorek's report of erotization in apes is also, of course, an objective observation.

In human cases a considerable number of striking objective results have been reported. In fat, sluggish subjects Retterer and Voronoff noted a loss of seven kilograms with improvement of strength, and Lydston a loss of forty pounds of "flabby fat" and transformation of a lethargic individual into an enthusiastic athlete. Stanley reported the clearing up of a considerable number of cases of acne and improvement of asthmatic conditions apparently as direct results of implants. The improvement in such conditions as asthenia and senile debility also involves an objective aspect. Stanley and Kelker noted a deepening of the voice, as did Lichtenstern together with growth of hair and resumption of sperm formation. Growth of public and axillary hair was reported by Lydston and Pfeifer, while Hunt remarked upon a considerable degree of restoration to brown of the grey hair of a man of sixty-five. Lisser's recent report of marked change in the character of the nails of a eunuchoid together with gain of seven pounds in weight in a single week is striking.

The foregoing observations leave no room for reasonable doubt that testicle grafting is capable of producing definite somatic changes and definite erotization. They seem to lay upon the conservative surgeon the duty of accurate determination of the best methods and of the possibilities and limitations of the procedure. The hesitancy of such men to enter this field is easily understood but its intrinsic difficulty or distastefulness does not obviate the scientific necessities in the situation. At the present stage of our knowledge it seems especially desirable that negative results as well as positive be placed on record.

PERSONAL INVESTIGATIONS

In the experiments herein reported eleven castrated rats varying in age from 119 to 256 days were placed in recording cages, previously described by Durrant (1924, 1925). The rats are placed in small retiring cages where they receive food and

water, from which they can make their way at will into revolving cylinders a foot in diameter. The apparatus, in short, consists of an adaptation of the old-fashioned "squirrel cage" much as described by Steward in 1898. The cages are free to turn in either direction and the revolutions are additively recorded by means of Veeder ratchet counters. Healthy, normal rats show a somewhat surprising degree of spontaneous activity under such conditions. In one case, for example, an individual young adult ran a distance of approximately 950 miles in 120 days. In a research previously mentioned (Hoskins, 1925) it was shown that castration reduced the activity during the most

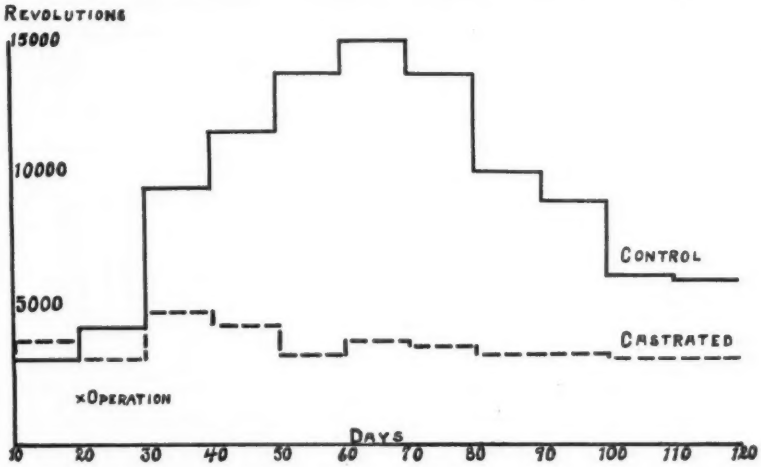

Fig. 1. Activity of normal and castrated rats as manifested by turning revolving cages one foot in diameter.

vigorous period of life from about 15,000 revolutions to about 3,800 per day. These results are shown in figure 1.

The activity of the castrated rats employed in the experiments herein reported varied from 770 to 5121 revolutions per day, with an average of 2175 and 2233 respectively in the two ten-day periods preceding the testicle grafting. In two instances the same rat was used twice, making thirteen experiments in all.

Two methods of grafting were employed. The material was obtained from healthy young adult rats. In eight cases the

Stanley method of implantation was used. The testicles were freed from the tunica and larger blood vessels and placed in a record syringe to which a hypodermic needle was attached. Through this needle the gland substance was introduced subcutaneously near the median abdominal line, about half way between the symphysis pubis and the lower end of the sternum. By shifting the position of the needle under the skin it was possible to distribute the gland material over a fairly large area without removing the needle. Ordinarily a single gland, weighing approximately one gram, was used, though occasionally both glands of the donor were introduced into the recipient. In five cases pocket implants were made. The skin was incised in the median line and the rectus abdominis muscles exposed on

TABLE 1

Average Daily Number of Revolutions Tabulated in Periods of 10 Days Each

Animal No.	Age in days when grafted	Days after castration	Nature of graft	2d period before	1st period before		1st period after	2d period after	3d period after	4th period after
74	128	57	S*	1200	1210		1321	1170	359	178
123	119	57	S	2200	2292		1884	2449	2447	1910
586	158	60	P†	2416	2474		1344	2170	1879	1689
485	185	55	P	770	1098		480	895	1121	1282
182	248	176	P	2047	1566		991	1866	1385	1575
197	154	83	S	2943	3752		2425	3345	3231	3434
28	161	84	S	1143	1362		1411	1449	1586	1553
28	215	138	P	1078	1216		1234	1166	1398	1241
159	157	83	S	1684	3734		4256	2431	2078	2536
151	157	83	S	5126	3343		5244	4644	6078	4451
151	256	182	P	2697	1966		2102	1927	1733	1490
216	150	83	S	1101	1410		1828	2219	2337	2818
114	169	103	S	3872	3614		3989	3066	3019	2595
		Average.....		.....	2233		2193	2215	2204	

GRAFT

*S—Stanley method. †P—Pocket graft.

each side. The points of fine scissors were introduced beneath the rectus sheath about 1 cm. from the median line and by spreading the points a pocket was made. The muscle was purposely scarified somewhat in the process. A testis was then removed from the donor, the tunica stripped off, the gland divided longitudinally and a half placed in each pocket. The pocket was closed by a single silk ligature through the fascia and the skin was closed with a silk ligature. In almost all cases the incision healed promptly without discharge. The animals for the most part have not yet come to autopsy, but

judging from inspection and palpation the grafts were largely or completely resorbed in all cases. There has been opportunity to corroborate this assumption in two instances by direct inspection at second operation. In one case of a Stanley implantation that has come to autopsy microscopic study of the tissues at the site of the injection showed practically complete absorption with only a slight amount of yellowish glandular debris to mark the site.

The results of the experiments as shown in table 1 and in figure 2 were consistently negative.

Since the completion of the study just described the experiment has been repeated twice on another animal with similar negative results, making the series total fifteen experiments in twelve animals.

A similar study has been made in case of three senile animals, the initial activity of which ranged from 40 to 160 revolutions per day. While this series is too restricted to have much significance, it may be mentioned in passing that, as shown in table 2, the results were also negative.

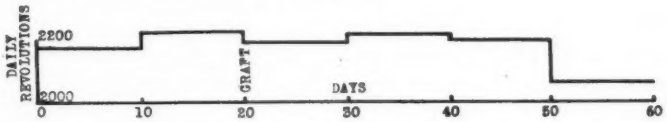

Fig. 2. Average activity of 13 rats in revolving cages before and after testicle grafting.

There are two possible explanations of these results. The most plausible is that the technic was inadequate and that the grafts underwent prompt necrosis without supplying a significant amount of the hormone. In similar studies with spayed female rats Wang (1923) showed that the activity was markedly increased by successful ovarian grafts. The other obvious possibility is that the cage method is inadequate to show the efficacy of the testicle hormone. This is rendered improbable, however, both by Wang's results with ovarian grafts and by the fact that castration results in a marked diminution of cage revolutions.

As suggested in an earlier paragraph, there is some probability that more effective results can be secured by testicle grafts when a certain amount of native testicular tissue is

already present. In Morris' case, for instance, the subject's own atrophic testes underwent considerable hypertrophy and with this was noted evidence of augmented hormone activity. In the three instances, however, of senile animals included in this study no better results were secured than with the castrates.

The study is being continued both with testicular extracts and with grafts implanted by a different method.

TABLE 2

Average Daily Number of Revolutions of 3 Senile Rats Tabulated in Periods of 10 Days Each

Animal No.	Nature of graft	2d period before	1st period before	GRAFT	1st period after	2d period after	3d period after	4th period after
9	S*	160	110		98	148	184	Dead
703	P†		40		0	10		
702	P	153	139		67	124	140	104

*S—Stanley method. †P—Pocket graft.

SUMMARY

In 15 experiments with castrated rats and 3 with senile subjects the activity as recorded in revolving cages was markedly below that of normal young adults. Testicular grafts consistently failed to bring about any significant improvement of activity.

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INTER-GLANDULAR ASSOCIATIONS (A STATISTICAL STUDY)

Preliminary Report*

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The opinion has frequently been expressed that the glands of internal secretion comprise a system of specifically interrelated organs. Many diagrams have been published to show the nature of the assumed associations. If the glands are interrelated, it is obvious that any disturbance of the normal balance of the system, either by disease or by design, would give an end result expressing the total disharmony rather than the direct response of individual structures to a single stimulus. It is clear, then, that a determination of the validity of the assumption can be arrived at only through an examination of normal material.

With this in mind, it was decided to test the assumption by a determination of the specific size (weight) correlations of the incretory organs in normal subjects, using the statistical method of partial correlation as the analytical procedure, and the weights of the thyroid, thymus, adrenals, pancreas, gonads and hypophysis of male and female adult albino rats as raw data. Several months were consumed in making and rechecking the multitudinous calculations involved.

The glands were removed from 121 male and 121 female rats 150 days of age. The animals were from the Experimental Colony Stock of The Wistar Institute. They had a common inheritance, were healthy, had never been mated, and had been raised under like conditions of diet and environment as described by Greenman and Duhring (1).

The method of analysis is described by Pearl (2) in his well-known book, "Medical Biometry and Statistics." The

*Through the courtesy of Doctor Frederick M. Allen, I am enabled to present this preliminary survey of the more significant points resulting from a biometrical analysis of the size inter-relationships of the glands of internal secretions. The full report is to appear in the Journal of Metabolic Research, of which Doctor Allen is the Editor.

numerical values resulting from the mathematical procedure indicate whether or not a given pair of organs (such as the thyroid and the adrenals) are associated in weight, independently of any influence assumed to be exerted by the other incretory structures and of any influence assumed to be exerted by the general factors determinative of size carried by the total body weight. They thus represent the presence or absence of specific weight association.

If correlation is present, a functional relationship on a quantitative basis can reasonably be concluded. On the other hand, the absence of specific weight correlation can not, of itself, be taken as indicating absence of specific functional relationship. While this limitation is a barrier to complete solution of the problem, it is no more an obstacle than is experimental interference with the function of the glands.

Now if the assumption that the glands of internal secretion comprise a system of specifically interrelated organs is correct, a definite specific correlation between each of the fifteen pairs which go to make up the system as studied here would be expected. This expectation is not fulfilled, for several of the pairs in each sex exhibit no specific weight association whatsoever. Therefore the assumption is invalid insofar as the interglandular weight relations are concerned. It may or may not be true with respect to the functional aspect, though evidence will be given shortly indicating that no functional correlation exists in such cases. Nevertheless the evidence is indirect and more suggestive than conclusive.

Various factors have contributed to the placing of the thyroid gland in the center of the stage of biological and clinical interest in endocrinological matters. An importance has been bestowed upon it which has tended to throw the significance of the other members of the group into the background. This is probably due to the facility with which thyroid disturbances in man are recognized, and their dramatic nature in comparison with the disturbances emanating from the other ductless glands. The biometrical analysis herewith reported has demonstrated that this opinion must be altered and the thyroid relegated to a minor role insofar as its participation in interglandular weight relation is concerned. There is no specific size

association between the thyroid and any of the other glands of internal secretion save the adrenals, at least in the normal albino rat at the usual level of thyroid activity. This restricted specificity establishes the hypothesis of Marine (3) and his co-workers of a thyroid-adrenal functional relationship on a firm basis.

Another incretory organ which is commonly thought of as participating in the determination of size relationships is the hypophysis. Strangely enough, in the normal adult animal there is apparently but little tendency for this organ to be correlated in weight with the other members of the group. Some degree of association with the ovaries in the female and with the pancreas in the male is exhibited, but these are small in degree. This lack indicates that hypophyseal function is either of little influence in the determination of size changes in the other ductless glands or that it is insensitive, as far as weight is concerned, to differences in quantity output of these organs within the usual range of their activity.

The stellar role hitherto held by the thyroid must be given to the adrenals. These structures are positively and specifically correlated, at the usual level of thyroid activity, with all of the other glands of internal secretion save the hypophysis in both sexes. The presence of such association between adrenals and gonads establishes the hypothesis of Riddle and his co-workers (4) of a functional relationship between the two organs on a firm and exact basis.

Similarly, the finding that the adrenals and thymus are specifically correlated in their weight relations substantiates the opinion of Jaffe (5) that these two structures are united in some sort of a functional association.

Although the incretory organs studied in this investigation are not directly specifically interrelated as a group, nevertheless several of the directly non-related pairs can be considered as indirectly associated through the intervention of a third member The major mediating influence in this indirect association emanates from the adrenals. These glands are apparently the pivotal organs on which depend the interglandular associations. They appear to be partial determinants of the degree of association between various pairs of other incretory organs, and

hence are collators of some of the interglandular activities. The conclusion is justified that the adrenal glands are an integrating agency binding together certain of the other incretory structures into an associative size relationship.

This influence is more general and more specific in the female than in the male. The degree of association is also closer in the former than in the latter. These facts, taken in conjunction with the finding that the adrenal-ovary correlation is considerably greater in degree than the adrenal-testis, indicate that adrenal domination of the endocrine system is more far-reaching and more intensive in the female than in the male.

In view of the fact that interglandular weight relations are largely conditioned by adrenal influence, it is not too much to suppose that the same holds true of the functional interrelations, at least insofar as quantity output is concerned. If this assumption is correct, and I see no reason why it should not be, it is probable that the glands of internal secretion, as a group, are no more directly and specifically interrelated in function than they are in size.

Since a complete analysis of the biology underlying this conclusion is given in the detailed report of the investigation, further elaboration in this place is unnecessary.

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SURGERY OF THE GLANDS OF INTERNAL SECRETION

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Pursuant to the fundamental studies of the role of the internal secretions, surgeons and internists alike have sought methods whereby to diminish or increase the activity of the glands of internal secretion. Surgeons have endeavored to accomplish these ends by transplantations and by excisions. In many cases these surgical procedures have been logical and beneficial; in some cases they have been illogical and useless.

THE ADRENAL GLANDS

Until the function of the adrenal glands is better understood there can be no definite indications for or against surgical procedures. While it is established that the adrenal glands are concerned in all of the major activations of the organism, in particular those which are increased or lessened by an increase or lessening of emotional activities, nevertheless ,what would appear to be a logical assumption that diseases which are associated with such general activations of the organism would be ameliorated by lessening the adrenal substances has not been entirely supported.

Fifteen years ago in the belief that such diseases as hypertension, cardiovascular disease, epilepsy, Reynaud's disease and neurasthenia might be ameliorated by a diminution of the adrenal substances I performed partial adrenalectomies in a group of apparently hopeless cases with the following results:

Epilepsy: Eleven cases of epilepsy were operated upon. Unilateral adrenalectomy alone was done in one case; adrenalectomy with partial thyroidectomy and division of the cervical sympathetics was done in seven cases; with ligation of the thyroid arteries in one case; with ligation of the thyroid arteries and section of the cervical sympathetics in two cases. In two cases the operation was followed by improvement which has persisted

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for 10 years; in another case the condition was improved for eight years, when the patient died; and there was slight improvement in four cases followed by a complete return of the disease.

During the past few years German surgeons have shown a marked interest in adrenalectomy in the treatment of epilepsy, this interest having been initiated by Fischer and Brüning. The basis for Fischer's belief in the efficacy of the operation was that excessive response of the muscle fibers to stimulation which is manifested in convulsions is due to a peripheral as well as to a central mechanism, and since in Addison's disease, for example, muscular asthenia is the outstanding symptom, he believes that the muscular activity is governed in the main by the adrenals. It is stated that Fischer's experimental studies to establish the point that the chromaphil substance is mainly responsible for muscular activity were undertaken in 1913 and 1914 but have not been published. In those researches he demonstrated that the cortex is the part of the adrenal concerned in muscular activity, a finding which is in accord with that of Carman, Elliott and ourselves regarding the dominant function of the cortex.

Brüning tested this conception in 14 cases of severe epilepsy and reported no mortalities, three cases under treatment, five cured, less intensive and less prolonged but more frequent attacks in one case and no beneficial results in five cases of long standing. Brüning's results, however, have not been confirmed by other reporters. Specht in particular repudiates the work of Fischer and Brüning and on the basis of an experimental study states that in part at least the failure of the operation is due to the fact that according to his experiments there is an early hypertrophy of the remaining adrenal, and of the remainder of an adrenal after partial resection.

On the basis of these collected experiences the value of the operation for epilepsy therefore would seem still to be "sub judice."

Cardiovascular disease: In three cases of cardiovascular disease adrenalectomy alone was preformed in one, as the result of which the symptoms were slightly relieved for nine years. In the other two cases adrenalectomy with partial thyroidec-

tomy was done in one and in the other adrenalectomy with partial thyroidectomy and resection of the cervical sympathetics. These last two patients were unimproved, both dying of apoplexy, one five months and one a year after operation.

Reynaud's disease: In three cases of Reynaud's disease, no improvement followed adrenalectomy. In two of these cases section of the cervical sympathetics was done also.

Neurasthenia: Four operations for apparently hopeless cases of neurasthenia were performed. In one adrenalectomy alone was followed by no improvement. In one adrenalectomy with partial thyroidectomy was followed by immediate improvement but there has been no further record of this patient after her discharge from the hospital. In two cases the operative procedure comprised adrenalectomy with partial thyroidectomy and division of the cervical sympathetics. One of these two patients was unimproved but the other recovered completely and during the eight years since operation has shown no return of the symptoms.

My total experience therefore has been 21 adrenalectomies for the conditions cited above with doubtful results in cases of epilepsy and neurasthenia, and practically negative results in cardiovascular disease and Reynaud's disease.

Transplantation of the adrenal glands has not been employed as a therapeutic procedure. Marine and others have shown however that adrenal glands which have been implanted in the abdominal cavity will function; and it is not difficult to believe that such a procedure might be adopted in cases of adrenal deficiency such as Addison's disease.

PITUITARY GLAND

The outstanding authority for surgery of the pituitary gland of course is Harvey Cushing and we can do no better than to quote his own conclusions regarding the present status of surgery as far as this one of the ductless glands is concerned. I quote from his most recently published summary "The Hypophyseal Syndrome from the Surgical Point of View" —a communication to the Third Annual Congress of the International Society of Neurology. He states that the lesions of the pituitary gland which pertain to the domain of surgical treatment are those which are associated with tumors, and he

gives the following brief statement regarding the existing status of the surgical treatment of tumors of the hypophysis: (1) Simple adenomas with a markedly excavated sella turcica can be best extirpated by an operation by the basal route without great risk and with the hope, often justified, of a sensible and immediate improvement of vision. (2) Tumors of Rathke's pouch ought to be exposed by the high route by an osteoplastic craniotomy, but a permanent cure can not be hoped for when the neoplasm has been extirpated. He states further that in addition to these two principal groups there are numerous intermediary cases, the diagnosis of which is very difficult and for which operative indications are less clear. If one undertakes a surgical operation, the degree of success is measured by the amelioration of the vision and its permanency. He emphasizes the point that the only means worthy of confidence for registering the results of surgical interventions on the hypophysis is the perimeter.

PARATHYROIDS

Transplantation of the parathyroids has not been done to any great extent, nor has removal of the parathyroid as a therapeutic measure. So far as I can see, there is in fact no clinical indication for the latter procedure. On the other hand the parathyroids are the "bêtes noires" of the surgeon in performing thyroidectomies. Studies by Gley and by Vassale and Generale first established the vital importance of the parathyroids. Pursuant to the work of these investigators Halsted's studies related these bodies to thyroidectomy in so far as they indicated the importance of a technique which should avoid the removal or damage of these glandules.

Every surgeon who has had any marked experience with thyroidectomies is but too familiar with the symptoms of parathyroid deficiency which indicate that the parathyroids have been inadvertently removed with the gland. It is interesting to note that we have never seen a case of parathyroid tetany in a male; and that it is usually exaggerated at the time of the menses. It should be added that parathyroid deficiency may be caused also by interference with the blood supply, by pressure of the surrounding parts as a result of trauma or infection or by contraction of the scar tissue. It is unfortunate that

the symptoms due to parathyroid disturbances are sometimes delayed, for they may occur at any time between six hours and three or four months after operation. It is not necessary here to discuss the symptoms. The treatment should consist, of course, first of all in the removal of the cause of the tetany. If it occurs within 24 hours after operation, we may properly conclude that it is due to the removal of the parathyroids or to interference with their blood supply. If it appears later, it is usually due to edema of the surrounding tissue, and if it is delayed for three or four months it is due to the interference with the blood supply of the parathyroid by the contraction of the scar tissue. When it is due to edema of the surrounding tissue the wound should be opened promptly in order that the edema may be lessened and the blood supply established at the earliest possible moment, and hyperemia by means of hot packs should be induced in order to increase the blood supply of the glands. In any case when the first symptoms appear, medication should be instituted at once.

During the past six weeks we have been using the hormone discovered by Dr. J. B. Collip of Alberta University and have secured as definite results as he secured with his experimental animals in both acute and chronic cases of tetany. Five acute cases have been treated with relief in every case. Relief of symptoms is usually experienced within twenty minutes to one-half hour after the intravenous injection of 1 cc. of the hormone. In one exceedingly acute case, in which not a single one of the classical symptoms of tetany was lacking, the first dose was followed within twenty minutes by a disappearance of the subjective symptoms. Three doses of 2 cc. each resulted in complete recovery. Among the chronic cases treated relief has been secured in about 85 to 90 per cent. In the cases in which Collip's hormone is not used the following measures are employed: Two grains of thyroid extract are given twice a day, ⅕ of a grain of parathyroid extract three times a day and 20 grains of calcium lactate every four hours. Five cubic centimeters of a 10 per cent solution of calcium chloride is given intravenously once a day for three days. If at the end of this period analysis of the blood shows a normal calcium content this medication is discontinued. If the blood calcium is below

the normal, then the medication is continued. If the patient has tingling of the fingers the dose of calcium lactate is increased to 40 grains. If the symptoms become alarming to the patient, ⅕ of a grain of morphin is given hypodermically and 20 cc. of a 25 per cent sterile solution of magnesium sulphate subcutaneously. With the latter dose particular pains are taken to spread the injection by using a long hypodermic needle and applying a hot water bottle over the site of the injection. It is a good precaution, to avoid any possibility that any of the solution may enter the veins, to inject the magnesium sulphate into the subcutaneous fat of the abdominal wall rather than into the muscle. This dose is repeated every five or six hours for three or four days, the calcium lactate and thyroid extract being continued for three or four days longer, after which the dose of these substances should be gradually decreased. Of course it is unnecessary to emphasize the necessity for watching the patient carefully for symptoms of magnesium sulphate poisoning.

THYROID GLAND

The surgery of the thyroid gland is almost entirely concerned with its removal. Implantations of the gland for myxedema and cretinism are occasionally performed, but no final judgment regarding their value can be made. My own experience has been limited and I can only say that the results up to the present time have seemed encouraging.

It is interesting to note in Halsted's splendid historical account of the operative treatment of goiter that up to 1883 there were reports of but 45 operations for goiter in America. Since the monumental work of Kocher, at whose clinic at the time of his death in 1914 approximately 5000 subjects of goiter had been operated upon, and the fundamental researches of Sir Victor Horsley laid the foundation for our present conception of the role of the thyroid gland, the surgical treatment of this organ has progressed with extreme rapidity. The problem with which the surgeon is primarily concerned is the treatment of hyperthyroidism. The removal of the simple goiter presents no problem. It is performed in the main for cosmetic reasons and in a sense may be considered among the simpler surgical procedures. The treatment of simple goiter and also the treatment

of carcinoma of the thyroid should be considered mainly as problems of prevention. In our own experience there has been a carcinoma of the thyroid in 139 cases among 6427 thyroidectomies and in about 95 per cent of these cases the carcinoma appeared in foetal adenomata. Moreover, about 10 per cent of all foetal adenomata seen at operation are cancerous. It follows that a foetal adenoma should always be removed, and fortunately it is the easiest of all types of goiter to remove. Simple adenomata are generally multiple but foetal adenoma is usually a well defined tumor and is present on one side only. Moreover iodin has no effect upon a foetal adenoma. In addition to the tendency to the development of cancer, adenomata often produce myocarditis and hyperthyroidism.

If foetal adenoma is malignant and can not be removed it is treated with radiation, but it should be removed if possible. A patient with an inoperable carcinoma of the thyroid gland will live without radiation for about a year. The length of life with radiation is still undetermined. In our own experience the mass has sometimes disappeared but in other cases radiation does not seem to be of any avail and we have no present criterion upon which to found a judgment as to which cases will respond favorably. When the patient is suffering from obstruction and resultant partial asphyxiation, a decompression operation will give temporary relief, the operation being followed by radiation. If myxedema develops in such a case it can be promptly met by the administration of thyroid extract.

As for the treatment of the patient with hyperthyroidism there is still a lack of uniformity of opinion regarding the relative merits of surgery and of radiation. On the basis of our own experience, however, we believe that surgery supplies the one method by which a controlled diminution of the gland can be secured. The amount of reduction of the gland by radiation can not be measured accurately, and if the patient comes to surgery later the difficulties of operation will have been increased by the radiation. From the economic point of view also, operation requires the minimum period of hospitalization and the final results are obtained more promptly.

A word should be said regarding the preoperative use of iodin which is so strongly advocated by Plummer and his asso-

ciates in the Mayo Clinic. The use of iodin in the treatment of hyperthyroidism has been employed by clinicians ever since iodin was first introduced into goiter therapy. It remained, however, for Marine and Lenhart in 1911 to establish the direct relation between iodin and different types of goiter. They found that iodin would convert a hyperplastic gland into a colloid gland and proved that in hyperthyroidism operation was dangerous in proportion to the hyperplasia of the gland. Marine therefore advocated the use of iodin in small doses in the treatment of hyperthyroidism and especially in the preparation of the patient with hyperthyroidism for operation. We tried out this method at that time with varying results and have tried it again since Plummer's advocacy of this measure, but have found that the results are uneven although in hyperplastic cases the operative risk is lessened.

From the point of view of the surgeon the problem with hyperthyroidism is rather a problem of management. No other type of case requires a higher degree of protection during the pre- and post-operative periods. The patient with hyperthyroidism demands protection against excessive metabolism, against the dangers of a weakened myocardium, against acidosis. To the surgical technic therefore must be added diminution of excessive metabolism and controlled environmental and dietary factors, protection of the internal respiration by the administration of fluids and glucose, reinforcement of the weakened myocardium by digitalization, the use of Lugol's solution in hyperplastic cases. When to these measures are added divided operation and a prolonged period of controlled hygienic regimen, the ultimate percentage of cures will be attained.

Our series includes 9445 operations upon the thyroid gland, among which 6636 have been for hyperthyroidism, the latter group including 3663 thyroidectomies and 2973 ligations. In the first 50 operations for hyperthyroidism the mortality was 16 per cent. At this moment we have a series of 333 ligations and 173 thyroidectomies without a death. In the latter series if we were to discount a death from cerebral embolism in a case of Parkinson's disease our series of thyroidectomies would be 226 since the last thyroid death. In these two series 454 of the operations have been performed in the patient's room without

moving him from his bed. In the treatment of tumors of the thyroid and the treatment of hyperthyroidism surgery has achieved one of its finest successes.

Finally it should be emphasized that in the treatment of the glands of internal secretion the surgeon is peculiarly dependent upon the laboratories. The laboratories must supply the basic facts upon which the plan of management is to be constructed.

Book Reviews

GOITER: NONSURGICAL TYPES AND TREATMENT. Israel Bram, 1924. MacMillan Co., N. Y., pp. 479.

Bram's book is a development of the thesis that goiter is preventable, all early goiters are curable, a large percentage of goiters that are treated surgically are perfectly amenable to non-operative procedures, and thyroidectomy is a failure in a large percentage of cases. The subject matter is derived partly from the authoritative literature and partly from a large personal experience.

It is maintained that the best ultimate results are obtained by an adequate division of all goiters into two classes: the non-surgical, comprising simple parenchymatous hypertrophy, colloid goiter, puberty hyperplasia and exophthalmic goiter; the surgical, consisting especially of cystic and adenomatous goiters. All goiters are amenable to early non-surgical treatment prior to encapsulation.

The chapter headings include the usual topics of books on goiter, such as anatomy, physiology, diagnosis and classification, with special chapters on the circulatory system, nervous symptoms and miscellaneous symptoms in exophthalmic goiter. The various diagnostic tests are clearly discussed and properly given a place strictly subordinate to accurate clinical study with special attention to the past and the existing condition of the patient. The adrenalin test is regarded as not reliable and may aggravate the symptoms. The basal metabolism test is appraised as an occasionally needed supplementary measure but ordinarily of little more significance than the pulse rate. The author's own "quinine test" is rated at 95% efficient in giving positive reactions (high tolerance) in "hyperthyroidism" and as valuable as an index to recovery. It is simple and inexpensive. The blood sugar test, while of some value, is viewed with disfavor in most cases as detrimental to the patient. Ten other tests of various degrees of promise are discussed. A considerable num-

ber of valuable data—largely empirical—are graphically set forth with diagrams in a chapter on "Vicious and therapeutic circles in exophthalmic goiter." While such diagrams have been unfortunately overdone in endocrinology, these form a succinct introduction to the section of the book that will be most valued by its clinical readers, namely, that on management. The treatment here is very full and explicit. Irrespective of one's opinion of the validity of Bram's general thesis, anyone having occasion to deal with goiter patients will find much of value. Hygienic measures, diet, local measures and drug treatment are emphasized and evaluated. A much needed chapter on psychotherapy is included. The book closes with an "appendix" listing 31 of the author's own papers from the periodical literature.

R. G. H.

OPOTHERAPIE ENDOCRINIENNE. LES BASES PHYSIOLOGIQUES, LES SYNDROMES, LA POSOLOGIE DE L'OPOTHERAPIE PAR LES GLANDES A SECRETIONS INTERNES. Guy Laroche, 1925. Masson et Cie., Paris, pp. 256.

The scope of the book is well indicated in the title. The author recognizes explicitly the desirability of basing organotherapy always upon a solid foundation of normal and pathological physiology. In view of our ignorance on many important points, the foundation afforded is necessarily often rather insecure, but an admirable selection of such material as is available has been made. In general the work is free from the credulous twaddle that one always fears to find in a book on endocrine therapy. As test cases, the thymus gland and the male gonads are dismissed with scant consideration. With the omission of this gladly spared portion of the literature, the book reflects very well the current conceptions of organotherapy. Its widespread use instead of the unreliable trade publications that are too often followed would add to medical sanity.—R. G. H.

VAGOTONIES SYMPATHICOTONIES NEUROTONIES. LES ETATS DE DESEQUILIBRE DU SYSTEME NERVEUX ORGANOVEGETATIF. A. C. Guillaume, 1925. Masson et Cie., Paris, pp. 281.

That an adequate knowledge of the physiology and pathology of the autonomic nervous system would go far in illuminat-

ing the field of diagnosis seems sufficiently obvious. That any important symptom complex can be satisfactorily resolved into its reflex elements is doubtful. Guillaume has essayed to bring together the significant data on vegetative neurology now available for practical application. He revises the older notions of the Viennese school in the light of more recent studies. Conditions of simple augmented or depressed irritability in the sympathetic and the parasympathetic systems are considered, with the signs of, and methods of detecting, each. The results of imbalance in the two systems are then considered. A final section is devoted to hormone factors in autonomic neurology. The book concludes with a well balanced bibliography selected from the world's literature.—R. G. H.

Abstract Department

The output of adrenalin in cerebral anaemia as studied by means of crossed circulation. Anrep (G. V.) & Doly (I. deB.), Proc Roy. Soc. (Lond.), 1925, **97 B**, 450-463.

The denervated heart of the heart lung preparation does not respond with an "adrenalin-like" effect when the blood flow through the coronary vessels is increased. This is true for widely varying concentrations of adrenalin in the blood. This preparation can be used for rough indications of an increased concentration of adrenalin in the blood provided the temperature is maintained constant. When used in crossed circulation experiments to perfuse the lower half of a second animal the isolated heart responds by acceleration to stimulation of the splanchnic nerve and to anemia of the brain of the perfused animal. This effect disappears after extirpation or denervation of both suprarenals.—G. E. B.

Resuscitation by epinephrin (Chloroforme et adrenaline. A propos de la reanimation experimental du coeur). Bardier (E.) & Stillmunkes (A.), Compt. rend. Soc. de biol. (Par.), 1925, **92**, 1048-1057.

Bardier and Stillmunkes succeeded with intracardiac injection of epinephrin in reviving dogs that had succumbed to chloroform anesthesia poisoning when the rhythm of the heart at death had been slow and irregular and the contractions extremely weak. Syncope, from the association of the epinephrin and the chloroform, often followed the injection, even when the contractions of the heart had become normal and the blood pressure had risen. The injection failed when it coincided with fibrillation of the heart or soon followed it.—J. Am. M. Ass., **84**, 1786.

The significance of the potassium ion for the adrenalin reaction. VIII. Kylin (E.), Klin. Wchnschr. (Berl.), 1925, **4**, 969-970.

The action of adrenalin is two phase, i. e., it normally raises, but may under certain conditions lower blood pressure. The K ion intensifies the lowering phase. Ca has the opposite effect.

—Chem. Abst., **19**, 2241.

The histopathology of Kala-azar in the hamster, monkey and man. Meleney (H. E.), Am. J. Path. (Boston), 1925, **i**, 147-168. 6 plates, one in colors.

A careful description of the histopathology of Kala-azar with special attention to the distribution of the Leishman-donovan bodies. The only features of interest to endocrinologists are the

observations that in the most advanced infections the parenchymatous cells of the **adrenals** become parasitized, and that the parasites are found in the interstitial tissue of the **testicle**.—J. P. S.

Adrenalectomy and morphine tolerance in rats. Rogoff (J. M.), J. Pharmacol. & Exper. Therap. (Balt.), 1925, **25**, 155.

Rats that survive indefinitely double adrenalectomy were not found to be more sensitive to morphine than normal rats. The rats that do not survive indefinitely removal of the adrenals are not considered fair test animals for determining morphine tolerance.
—G. E. B.

The action of adrenalin on the pregnant human uterus. Rucker (M. P.), Southern M. J., 1925, **18**, 412 (June).

Hysterograms obtained by connecting a Voorhees bag within the cervix to a recorder writing upon a kymograph were made upon twenty patients, nineteen of whom were at term and one in the fifth month of pregnancy. Sixteen showed a prompt cessation or diminution in strength of uterine contractions for a period of from 9 to 30 minutes after a hypodermic injection of five minims of adrenalin. In four cases there was no demonstrable effect. In no case was there an increase in the force or frequency of uterine contractions. There was no change in the subjective pain. The inhibitor effect of adrenalin upon uterine contractions is heightened when the same dose is combined with novocain in sacral anesthesia.
—Author's Abst.

The influence of calcium and potassium on the response of the isolated frog heart to epinephrin. Salant (W.), Washeim (H.) & Johnston (R. L.), J. Pharmacol. & Exper. Therap. (Balt.), 1925, **25**, 75-89.

Excess of calcium in the perfusing solution slightly increased the effect of moderate amounts of epinephrin and inhibited the action of small doses when the heart was normal. It was inactive when the calcium was greatly reduced or totally removed. When the amount of calcium was small epinephrin was effective provided the potassium had been correspondingly reduced. When a sufficient amount of calcium was present in the perfusing medium an increase of potassium greatly augmented the action of epinephrin. In potassium free solutions epinephrin became inactive after a brief period of stimulation. Changes in permeability are suggested to account for these effects.—G. E. B.

Intracardiac epinephrin injection. Schapiro (A.), Zentralbl. f. Chir. (Leipz.), 1925, **52**, 798-799.

In Schapiro's patient, aged 75, complete collapse occurred after excision, under general anesthesia, of an extensive carbuncle on the neck. Camphor subcutaneously, strophanthin intravenously, were

ineffective, also artificial respiration, etc. Then epinephrin was injected into the heart muscle, with restoration of the pulse in 20 seconds and return of the normal color of the skin and regular breathing. Complete recovery followed after a few days under heart stimulants. Injection of epinephrin directly into the heart muscle is advised in all cases of acute, particularly postoperative, arrest of the heart action.—J. Am. M. Ass., **84**, 1707.

Calcemia in tuberculosis: adrenalin and the fixation of calcium. Sergent (E.) & Binet (L.), Rev. path. comp. hyg. gén., 1925, **25**, 63; Bull. soc. hyg. aliment., 1925, **13**, 178.

Free Ca determination in the blood serum of 30 pulmonary tuberculous patients by G's method showed 100-110 mg. per liter. In tuberculous patients who were in fairly good general condition, who suffered from fibrous tuberculosis or who had tuberculous cervical adenitis, the Ca content was 120-130 mg. per liter. Rats subjected to Pappenheimer's No. 85 rachitigenic diet showed no signs of rickets when given subcutaneous injections of adrenalin, which seems to act as a fixing agent for Ca and acts similarly to phosphates and to certain oils by permitting the organism to utilize the ingested Ca.—Chem. Abst., **19**, 2238.

Heterotopia of adrenal in liver and kidney. Weller (C. V.), Am. J. M. Sc. (Phila.), 1925, **169**, 696-712.

Weller reviews the literature and reports 4 new cases. By heterotopia of the adrenal in liver and kidney is meant the developmental inclusion of the adrenal in or beneath the capsule of one of these organs. Inflammatory adhesions and the lesser aberrant adrenal masses are not included in this definition. Duplication of the adrenal may be present. Of adrenal-renal heterotopia one new case is added. This condition occurs chiefly in males and is usually bilateral. Three new cases of adrenal-hepatic heterotopia are added. Although presumably the more common of the two, this has received but little mention in the literature. Adrenal heterotopia is usually associated with a persistent thymus and other evidences of the thymico-lymphatic constitution, and frequently with the asthenic habitus. It is an evidence of constitutional pathology. In 2 of the 13 renal cases reported death has resulted from diabetes. Most of the subjects of adrenal heterotopia have died at a relatively early age. The incidence of tuberculosis and other infections is high. The danger of reducing the adrenal tissue inadvertently in a nephrectomy should the kidney contain a heterotopic adrenal is stressed.—R. G. H.

Discussion of the ductless glands. Barker (L. F.), Proc. Ass. Am. Physicians, Washington, D. C., May 5-7, 1925.

Clinicians are apt to consider this type of thought as hypothetic or speculative. The feeling is often expressed that there should

be no hypotheses or theory in endocrinology, only facts. There is nothing more erroneous than that idea. To get at facts you must first have some theory. On the other hand, you must know when you are speculating. The great injury is done by assuming that hypothetic constructions are established principles; but there is no reason why we should not make use of hypotheses as such. Such theories are extremely useful in directing experimental work, and in clinical work as regards controlling observations and keeping up records. The interest in endocrinologic studies all over the world is amazing. Three thousand works appear every year. Some men should sift facts and bring certain ideas together, presenting them in a clear way. Endocrinology is of interest to every physician and every surgeon because the endocrine organs have to do with control of phenomena in every part of the body. A rational explanation of these phenomena is highly desirable. This domain is as yet essentially an empiric one. The majority of conceptions have come from clinical men who have made empiric observations and reported them. If one thinks of the contributions made clinically—Addison's work on the suprarenal glands; Kocher's studies on cachexia thyreopriva, and the work of Marie on myxedema—one can gauge the importance of empiricism to clinical men. Rational explanations are coming from scientific men in laboratories, but their number is, as yet, small. The attempt has been made to put forward as established principles statements that were nothing more than hypothetic constructions. We need more skepticism and less blind confidence, but the skepticism should be an eclectic skepticism.

A word about uniglandular and pluriglandular theories: The glands are undoubtedly related and affect one another. Theoretically, every syndrome must be pluriglandular, but as yet syndromes are predominantly uniglandular and the study of them is as such rather than by pluriglandular involvement. One point is very striking in the latter respect: A great variety of pathologic phenomena can be made to disappear by the substitution product from a single organ. The general therapy is uniglandular in principle, even though scientific study shows a whole series of processes. Theoretically, the number of endocrinopathies is enormous. Each gland has six possible conditions: normal, hypofunctioning, hyperfunctioning, dysfunctioning, and the combinations of hypofunctioning and hyperfunctioning. If there are nine glands giving internal secretions, the possible combinations mathematically worked out could cause 10,770,095 different syndromes. Dr. Abel spoke of 15 secreting glands; and if we were to estimate all the possible combinations of these we should have a reductio ad absurdum. Some simplifying process must be arrived at or the outlook for therapy would be nearly hopeless. One can imagine the joy of commercial drug houses; they could put out more than 46,000 stock preparations. We must not, therefore, go too far into pluriglandular

therapy. Fortunately, among all the pluriglandular formulas on the market, commercially, only one substance is likely to have any effect; that is, **thyroid.** Therefore the administration of these pluriglandular mixtures which are so much advertised will probably do very little harm as long as the amount of thyroid is not enough to harm the patient. As soon as the public learns this, what Dr. Abel calls "the stampede to the pluriglandular gold fields" will subside What the future of this work will be it is rash to prophesy. Clinical syndromes will have to be revised, and we shall have to study gland structure until we have reached a point in biochemistry at which we have each active principle. The outlook of the subject for the future leads us to believe that there will be found endocrine factors to control growth and to modify constitutional disposition by the application of pharmacodynamic combinations. I do not think that anyone can say that more harm than good has come from the study of endocrinology. That is a false statement. There is much honest work being done despite bombastic theory. We must set our faces against ignorant credulity, on the one hand, and cynical incredulity, on the other. Let us all work together to advance knowledge in this important field.—J. Am. M. Ass., **84,** 1867.

Endocrinology in pediatrics, with special reference to the hypoplastic-dyspituitary type of child. Dowd (H. L.), Arch. Pediat. (N. Y.), 1924, **41,** 801-816.

Children of the status thymico-lymphatic type, frequently overweight, sometimes tall, slender and loose-jointed, are a difficult problem of adjustment. The nature of their growth and development renders them frequently self-conscious, inadequate, prone to injury and with a low resistance to infection. It is better to study their internal secretions, and to administer the appropriate glandular extracts than to neglect these glands and rely entirely on measures relating to diet and hygiene and correction of physical defects. Eight case reports from the Endocrine Clinic of Bellevue Hospital are included.—M. B. G.

Nature of internal secretion. Harms (J. W.), Deutsche med. Wchnschr. (Berl.), 1925, **51,** 631-633.

Harms traces internal secretions down to the division of the ovum (**harmezymes**). Later on **harmozones** regulate the differentiation and growth of the organism. After maturity the true **hormones** direct the metabolism. Their action is usually bound to a closed circulation. Yet the estrual cycle even in the Turbellaria is induced by the **gonads.** The **thyroid** begins to be differentiated in the human embryo in 20 days, the lobes of the **pituitary** in 3 to 4 weeks, the **thymus** in 2 months, the cortex of the **suprarenals** after the fourth week. The gonads act after one and a half months. Metamorphosis occurs in the human embryo in the second month.

It is impossible to differentiate the endocrine glands according to a catabolic or anabolic action. Even the thyroid has both. Harmozones play an important role in the differentiation of races: bulldogs with hyperfunction of thyroid, and greyhounds depending on the pituitary. The development and regression of some malignant tumors depends on the endocrine glands, especially the cortex of the suprarenals and the gonads. All the higher animals are to a certain extent bisexual. Changes of sex occur physiologically in a starfish (Asterina gibbosa) from the male to the female and in the swordfish (Xiphophorus) in the opposite direction. Castrated male toads lay eggs after a transformation of Bidder's organ, which may be enhanced by feeding with lecithins and other substances. The regressive phase of the organism may depend also on other endocrine glands—not only the gonads, although the author had excellent results with the transplantation of the latter in old dogs and guinea pigs. The success is more frequent in males. The normal senescence leading to death is due to the destruction of ganglion cells.

—J. Am. M. Ass., **84**, 1880.

Obesity in children, with special reference to carbohydrate metabolism and its modification by the administration of certain ductless glands. Langmead (F. S.) & Calvert (E. G. B.), Lancet (Lond.), 1924, **ii**, 1111-1115.

The authors point out that clinically many obese children are diagnosed as subjects of **dyspituitarism** on insufficient grounds. After the onset of puberty these children appear perfectly normal. The authors investigated 8 children, 4 boys and 4 girls. Two of the boys showed rudimentary sexual development. Two of the girls, aged 10 and 13 years, respectively, were sexually precocious. In the girl aged 10 years the precocious overgrowth followed encephalitis lethargica. It was only when obesity was accompanied by disordered physical or mental growth that it could be considered pathological. Obesity, such as that under consideration, may be due to a pituitary tumor, which if large enough, provokes particular signs of pressure. In none of the 8 cases investigated, however, was this so. Investigation of the pituitary fossa by x-rays was of help in 2 cases of the 8. Varying amounts of sugar up to 300 gm. were given by mouth, and in only one subject was glycosuria provoked. The authors consider this pathological. The blood sugar of these patients after varying amounts of glucose showed a variety of curves. Nothing characteristic was noted, but all were abnormal. In order to study the modification of the blood sugar curves by the administration of endocrine products, 4 patients were selected. These were 3 boys aged 10, 11½ and 14 years, respectively, and one girl aged 13 years. In the two younger boys the obesity was accompanied by genital hypoplasia, but there was no mental backwardness; the 2 older children were examples of obesity with over-

growth but with normal sexual development. It was found that in the 2 younger boys the giving of 2 grains of posterior pituitary desiccated substance 3 times daily caused the blood sugar curves to become perfectly normal. This favors the view that in cases of hypopituitarism it is the posterior lobe which is chiefly concerned with the altered carbohydrate metabolism. Pituitrin had less influence. In the third boy, with more normal general development and with normal sexual development, the anterior lobe was that which had the correcting effect. The slightly inferior influence in the blood sugar curve of the whole gland substance in the above 3 patients appears to indicate that in these cases the good effect on carbohydrate metabolism obtainable by giving the appropriate gland substance may be counteracted to some extent by combining it with the extract of the other lobe. It would appear to the authors also that pituitary gland substance given by mouth is not inert. Considering the patients generally, whole gland gives quite good results. Giving small doses of **thyroid** seems to amplify the effect of the pituitary gland. Thyroid gland may reduce weight in these patients, but does not restore carbohydrate metabolism to normal. When the blood sugars were reduced to normal considerable clinical improvement took place in the patients.—Med. Sc., **11**, 427.

Effect of *d.* and *l.* suprarenin, pituitrin and pilocarpin on the mineral balance of the lymph. Peterson (W. F.) and Hughes (T. P.), J. Pharmacol. & Exper. Therap. (Balt.), 1925, **25**, 137-138.

Adrenalin causes early acidosis, followed by alkalosis; hyperglycemia followed by hypoglycemia; early lessening of the phosphate level followed by a later increase. The calcium, potassium and sodium levels are not constant. Dextro-suprarenin and levo-suprarenin give similar results. Pituitrin causes the lymph flow to fall markedly. The phosphates, calcium, sodium and magnesium are increased, while potassium is diminished. Pilocarpin causes the phosphates to be increased while sodium, magnesium and potassium are diminished.—G. E. B.

Childhood inadequacy in relation to the internal glandular system. Timme (W.), Am. J. Psychiat., 1925, **4**, 499.

A large group of infants is characterized by hypoplasia of important structures, the vascular system, **suprarenals, pituitary, thyroid** and **gonads**, with large lymphoid organs. These children have certain inadequacies due to structure, to biochemical changes and to glandular insufficiency, which even in later life can be recognized. There is a tendency for the condition to be compensated spontaneously by over activity of the endocrine organs which leads to bodily changes. Timme calculates that there are some 720 combinations of inadequacies, all depending on the primary hypoplastic condition. Some of these inadequacies may be intellectual, emotional or be-

havioristic. These are the patients who are referred to the psychiatrist or to the psychologist. Some of these children may go on to dementia precox; it is impossible to classify which.

—Am. J. Dis. Child., **29**, 854.

The ovarian hormones (Les hormones ovariennes). Courrier (R.), Rev. franç. d'endocrin. (Par.), 1925, **3**, 94-101.

Courrier, working with guinea pigs, confirmed earlier observations that follicular fluid causes a marked reaction in the vaginal epithelium. He adds the observations that the fluid administered to a female late in pregnancy evokes the vaginal reaction in the fetuses and that the fluid is efficacious when given by vagina.—R. G. H.

Ovary and thyroid function (Comportamento dell' ovaio in rapporto alla funzione tiroidea). Dal Collo (P. G.), Folia med. (Napoli), 1924, **10**, 831-839.

In completely developed female dogs from the histological viewpoint ovaries are not influenced by thyroid modifications; common histological experimental methods are insufficient to demonstrate the functional relation between ovary and thyroid as they appear in the clinic.—P. M. N.

Arthritis from ovarian insufficiency. Fliegel & Strauss, Zentralbl. f. Gynak. (Leipz.), 1925, **49**, 633.

Fliegel and Strauss have long made observations similar to Menge's ovariprival arthropathy in women at or near the menopause, likewise in younger women and, far less often, also in men, particularly in the middle forties. Unlike Menge, they regard this affection of the joints as arthritis deformans. They ascribe it to endocrine disturbances, especially of the generative glands and the thyroid; the favorable results of their treatment of true arthritis deformans with iodin preparations support this view.

—J. Am. M. Ass., **84**, 1609.

The female sex hormone and gestational gland. Frank (R. T.) & Gustavson (R. G.), J. Am. M. Ass. (Chicago), 1925, **84**, 1715-1719.

Frank and Gustavson summarize their most important conclusions thus: Each sex cycle is preparatory to gestation, the normal sex cycle being the fertile one that leads uninterruptedly to parturition and lactation. An abortive cycle occurs when pregnancy fails to develop. Soon after ovulation the anabolic phase ceases, a catabolic period succeeding it. In most forms the catabolic period is involutionary. In the primates this period is destructive (menstruation). The endocrine factors producing the cyclic changes are successively supplied by the **follicle, corpus luteum** and **placenta.** To emphasize this continuity, the authors propose the name of the ges-

tational gland for this triad (follicle, corpus luteum and placenta). By substitution (subcutaneous injection) with lipoid extracts of these glands (follicle fluid, corpus luteum, placenta) they have obtained in female castrates or in immature animals alike: (a) premature sex development (pubertas precox); (b) hyperplasia of the tubular system and mammae, especially marked in rabbits; in castrates they have noted (c) in rats, vaginal spreads characteristic of estrus, together with hyperplasia of the duct system; (d) in rats, treated with potent extracts, typical estrual contractions of the uterus suspended in Locke's fluid. The active substance has been sufficiently concentrated to produce physiologic results in a total dosage of 2.25 mg. (0.00225 gm.). The sex hormone is a specific substance elaborated by the gestational gland, taken up by the lymph and blood stream and selectively utilized only by Müller's tract and the mammary glands. The chemistry of the sex hormone is not fully determined.—A. M. A.

So-called stimulating irradiation of ovary. Geller (F. C.), Zentralbl. f. Gynäk. (Leipz.), 1925, **49**, 1013-1018.

Geller states that after weak irradiation of the ovary in rabbits the histologic picture showed no certain signs of stimulation, but in almost every case degenerative changes were evident in the ova and follicles in all stages, without manifest or regular predilection for the ripe follicles.—J. Am. M. Ass., **85**, 79.

The action of weak irradiation of the ovary in the light of animal experiments. Stimulative irradiation of the ovary and temporary sterilization (Ueber die Wirkung schwacher Eierstocksbestrahlung auf Grund tierexperimenteller Untersuchungen. Ein Beitrag zur Frage der Eirstocksreizbestrahlung und der temporären Sterilisierung). Geller (F. C.), Strahlentherapie (Berl. u. Wein), 1925, **19**, 22-61.

After a résumé of the chief literature on the subject the author describes his own experiments. These were carried out on rabbits and rats, and a full description, with photographs, is given of the appearances found. He concluded that under an exposure of 5% of the skin erythema dose the ovary shows no alterations. With 10% there was a diminution in size and number of primary follicles, whereas follicles in a more advanced stage did not differ from those of the control animals. With 20-30% the ovaries were usually smaller than those of the controls; atresia of follicles was increased and affected all stages of follicles. Primary follicles were always (and very early after irradiation) much reduced in numbers, and such as were present were regenerated. At a later date young ripening follicles were found, though these frequently showed degenerative changes. The interstitial gland substance was equally developed in irradiated and control animals. After irradiation of

uterus and ovaries or uterus alone with 5-10% of the erythema dose the uterus showed no change, but after 20-30% there was definite hypertrophy, particularly of the mucosa, in which there was a more or less pronounced decidual reaction. With irradiation of the ovaries alone this uterine hypertrophy sometimes was wanting. In about 75% of the irradiated animals the weight ratio was increased and growth in length was diminished. No changes were observed in secondary sex characters, nor was there, histologically, any evidence of retrogression of the **hypophysis.** These results are then compared with those observed clinically in the human subject. There is a good bibliography.—Med. Sc., **12,** 172.

The action of testicular extracts on the circulation of the blood (Uber die Wirkung von Hodenextracten auf den Kreislauf des Blutes). Hahn (C.), Skandin. Arch. f. Physiol. (Leipz.), 1925, **46,** 143-170.

An alcohol extract of rabbit testicles injected intravenously caused a rise in blood pressure. The ether soluble fraction of the alcohol extract gave similar results. This effect was absent in pithed animals, indicating that the action is by way of the vasomotor nerve centers. The alcohol extract reduced the amplitude of the isolated beating heart while the ether fraction stimulated the heart musculature. In the frog the ether fraction caused vasodilation of the extremities.—G. E. B.

The production of spermatoxins. Kennedy (W. P.), Quart. J. Exper. Physiol. (Lond.), 1924, **14,** 279-283.

Six male and 6 female guinea pigs were injected intraperitoneally twice weekly with suspensions of guinea pig sperm. It was found that both males and females were sterilized. The antibody was more potent or produced in greater quantity by the males. Degenerative changes were found in the testes of some injected males, but were not seen in others. The above phenomena can be produced in a more marked degree by using the animal's own spermatozoa.—R. G. H.

Corpus luteum extracts and ovulation in the rabbit. Kennedy (W P.), Quart. J. Exper. Physiol. (Lond.), 1925, **15,** 103-112.

Twenty-five female rabbits were injected intravenously with saline extracts of corpus luteum. It was found that such extracts in sufficient dosage inhibit ovulation. Long continued dosage with these extracts may be correlated with more or less marked degenerative changes in the ovary, and to a progressively less degree in the liver and **adrenal** glands, none being observed in the kidney. In the experimental animals in which the point was tested, ability to ovulate was not recovered in 3 months from the cessation of treatment. The fertility of the male controls was not impaired by

parallel treatment. The toxic effects produced were insufficient to cause convulsions or death.—R. G. H.

The sexual glands and metabolism. I. Influence of castration on nitrogen and gaseous metabolism. Korenchevsky (V.), Brit. J. Exper. Path. (Lond.), 1925, **6**, 21-35.

In most cases removal or hypofunction of the sexual glands in animals or men is followed by increase in weight and accumulation of fat ("fat" castratus or eunuch). However, in approximately 40% of cases, castration or hypofunction of the testes and ovaries does not produce this effect ("thin" castratus or eunuch). Korenchevsky's experiments showed that both nitrogenous and, in most cases, gaseous metabolism were decreased after castration in "fat" castrated dogs. In "thin" castrated dogs this fall was usually less pronounced or absent; moreover, the gaseous metabolism was sometimes considerably increased. Nitrogen metabolism of fasting dogs and rabbits was much lowered after castration in all the cases investigated, but the gaseous metabolism did not change, was a little decreased, or was even increased. The fall after castration in the nitrogen metabolism of a fasting animal when compared with that of the same animal when fed is always much greater; the converse was noticed in the gaseous metabolism. All these facts show that not only accumulation of fat but also retention of protein in the body are the causes of the increased weight of "fat" castrati. Korenchevsky's and other experimental and clinical data suggest the presence of specific gonadal hormones, which influence the body metabolism. Whether the sexual hormones influence metabolism directly or indirectly through the other glands of internal secretion is not known. It is suggested that the results of castration may be due not only to the direct influence upon metabolism but also to the secondary changes in the thyroid, hypophysis, adrenals and pancreas, as well as to the varying degree of functional efficiency of these glands before castration.—H. L.

The sexual glands and metabolism. II. Influence of emulsions of testis and prostate upon the nitrogen metabolism of rabbits. Korenchevsky (V.) & Carr (M.), Brit. J. Exper. Path. (Lond.), 1925, **6**, 74-83.

Sixteen nitrogen metabolism experiments were performed on 6 rabbits, into which freshly prepared homologous emulsions of kidney, testis and prostate were injected. Testis or kidney emulsion when injected subcutaneously into rabbits slightly decreased the nitrogen metabolism during the period of injections, and in most cases during the succeeding 6-9 days. This effect of testis emulsion cannot be considered specific, because of the similar results obtained with kidney emulsion. An emulsion of prostate, alone or in combination with testis, when injected in the amounts given in the above

experiments, increased the nitrogen metabolism up to 11%, particularly during the 2 or 3 days following the period of injections. No difference was found between the reaction of castrated or of non-castrated rabbits. Since earlier experiments with prostate emulsion on dogs gave somewhat similar results to those on rabbits, it is suggested that the prostate forms a hormone that influences nitrogen metabolism.—H. L.

Regeneration of ovary. Pettinari (V.), Compt. rend. Soc. de biol. (Par.), 1925, **92**, 1294-1307.

Pettinari made bilateral implantation of ovarian grafts in a female dog 16 years old. She cast a litter 15 months after the operation. Removal of the ovaries a month afterward resulted in the death of the animal. No grafts were found at the necropsy; the ovaries presented a normal aspect, while at the time of the grafting they were in a stage of sclerosis and cystic degeneration. Histologic examination showed regeneration in a previously senile organ.—J. Am. M. Ass., **85**, 309.

Clinical studies on the urine of eunuchs. Shen (T. C.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925 **22**, 408-409.

Creatinuria has been reported in eunuchs. In 4 subjects cases carefully observed this was not confirmed nor were any peculiarities noticed.—J. C. D.

The gonads and sex physiology. Stockard (C. R.), Proc. Ass. Am. Physicians, Washington, D. C., May 5-7, 1925.

The sex glands are extremely complex when compared to the rest of the glands of internal secretion. They are the only glands of internal secretion that exist in the vertebrates and invertebrates in the same form. These glands have definite effects on other structures. During the embryonic period they influence the development of the internal and external genitalia. They are dormant from birth to the prepubertal stage, and then bloom out as the factors causing secondary sex characteristics. During growth and sex development they regulate the shape of the head and the height of the body. These glands have a rhythmic development, the periods of which repeat themselves. The chief evidence that these glands have an internal secretion is their effects on the organism. The problem of castration influences this question. We are apt to think of transplantation experiments as something modern, but in 1672 John Hunter transplanted testes in chickens and got some effects. Many workers have produced experimental feminization. They have transplanted ovaries into males and testes into females. These experiments have brought out considerable evidence that there exists an antagonism between the male and the female gonad. The problem of hormone production is a very different matter in the testes

to that in the ovary. The antagonism between the ovary and the testis is interesting and important. In the differentiation of sex we express the female character as the X chromosomes. The chromosomes have to do with the stem, or sex, determination, which is established at the time of fertilization of the ovum, at which time there are either two X chromosomes or only one. Differentiation of sex is a developmental problem, and has to do with secondary sex characteristics. It may be inhibited or charged by castration, but the chromosome influence is irreversible and immutable. The specific hormone effect produced by the gonads may act secondarily on other endocrine glands. The results of some experiments are spectacular, but they are of no use unless they are standardized. In attempting to work out an accurate method by which the results of experiments can be measured, we have started by working out a guinea pig unit which is standardized. Later we hope to be able to work out a human standard.—J. Am. M. Ass., **84**, 1867.

The pituitary and the female sex organs. Aschner (B.), Med. Klin. Berl.), 1924, **20**, 1681.

After extirpation of the pituitary gland or of its anterior lobe, there was a complete arrest of the growth in length and in mental development, persistence of the juvenile fat and lanugo, and infantilism of the sex organs. Extirpation during pregnancy was followed by abortion. In adult animals changes of the sex organs were obtained only after injuries of the diencephalon, not after extirpation of the pituitary.—Physiol. Abst., **10**, 113.

Concerning the microscopic structure of the hypophysis cerebri in acromegaly. Bailey (P.) & Davidoff (L. M.), Am. J. Pathol. (Bost.), 1925, **1**, 185-207.

Bailey and Davidoff prefer the terms "alpha" and "beta" cells to the more common terminology of acidophilic and basophilic cells in the anterior lobe of the hypophysis. The alpha granules are large and distinct and are stained intensely by eosin, acid fuchsin, neutral ethyl violet, etc. The beta granules are finer and less distinct, are more difficult to stain, but can be displayed by alum hematoxylin, kresofuchsin, acid violet and aniline blue. The relative numbers of alpha and beta cells in different hypophyses are most valuable. The authors report 4 cases of acromegaly, with detailed descriptions of the cytology of the anterior lobe in each case. They conclude that in those cases of acromegaly at least in which the gland reaches a size sufficient to demand operation, a constant pathological change takes place in the pars distalis of the hypophysis cerebri, consisting essentially of an adenomatous formation composed of alpha cells. The normal acinous structure tends to be lost; the cells lie in loose masses practically without stroma; the nuclei vary greatly in size and as many as half a dozen may be

present in one cell; the cells contain alpha granules which are finer than the normal alpha granules and which tend to collect at the periphery of the cytoplasm.—J. P. S.

The hypophysis and basal metabolism (Hypophyse et métabolisme basal). Pareja (J. M.), An. Fac. de Med., 1923, **8**, 1102-1117.

Basal metabolism is increased in **acromegaly** and in **gigantism**, decreased in **Frölich's syndrome** and in **diabetes insipidus.** Diseases of the pituitary are frequently associated with those of other endocrine glands, which also influence the basal metabolism.
—Physiol. Abst., **9**, 599.

Visual fields in pituitary disease—A case report showing the influence of endocrine therapy. Rowland (W. D.), Boston M. & S. J., 1924, **191**, 977-981.

The case is described of a woman of 25 whose clinical condition and laboratory findings after elaborate special study indicated pituitary involvement. She had suffered from headache for 4 years. Her basal metabolism was 25% below normal. Her vision of Sept. 8 was: Dist. vis. R., 10/12; Dist. vis. L., 5/40. She was given anterior lobe pituitary "extract"—dosage not specified. On May 3, following, her vision had become: Dist. vis. R., 10/10; Dist. vis. L., 10/12. The basal metabolism had become normal.—R. G. H.

Gallbladder and pituitary (Gallenblase und Hypophyse). Schöndube (W.), Klin. Wchnschr. (Berl.), 1925, **4**, 640-643.

Schöndube reports on the results of the pituitary action on the gallbladder found by Kalk and himself. Subcutaneous injection of an extract from the posterior lobe of the pituitary provokes in healthy subjects in 25 or 30 minutes a flow of pure gallbladder bile. Its concentration is higher than with any other (magnesium sulphate or peptone) method: in healthy subjects more than 200 Hijmans van den Bergh's units. The gallbladder concentrates the liver bile up to ninety-fold. In many cholecystitis patients the concentration is less and the time of appearance of the dark bile is delayed or shortened (excitability). In many of them the "pituitary reflex" is negative. He attributes the contraction to a mild stimulation of the vagus.—J. Am. M. Ass., **84**, 1704.

The pathology of the hypophysis. I. The presence of abnormal cells in the posterior lobe. Simonds (J. P.) & Brandes (W. W.), Am. J. Pathol. (Bost.), 1925, **1**, 209-216. 1 plate.

The authors report 8 cases of a peculiar lesion observed in the posterior lobe of the hypophysis consisting of a group of large abnormal, round, oval or polygonal cells whose cytoplasm stained bluish-purple and was faintly granular, and whose eccentrically placed nuclei were either deeply stained and pyknotic or pale and

apparently undergoing karyolysis. These masses of cells, although actually small, were relatively large when compared with the size of the posterior lobe itself. The nature of the lesion is not clear, although it is not believed to be neoplastic. Nothing in the clinical histories or physical findings in any of the cases could be definitely associated etiologically with this lesion.—J. P. S.

The pathology of the hypophysis. II. Lymphocytic infiltration. Simonds (J. P.) & Brandes (W. W.), Am. J. Pathol. (Bost.), 1925, **i**, 273-280. 1 plate.

Twenty-one cases of lymphocytic infiltration of the hypophysis are reported, among over 200 glands examined in serial sections. The lesion occurs most frequently in the middle lobe, and appears in four more or less distinct forms: (a) those in which the area of lymphocytic infiltration was in immediate relation to one or more masses of colloid; (b) those in which the mass of lymphocytes were closely associated with a blood vessel and frequently resembled a potential lymph gland; (c) those in which the lymphocytes diffusely infiltrated the tissues involved without relation to blood vessels or colloid; and (d) those in which the infiltration was definitely perivascular. Three of these forms were believed to be the result of reaction to a local stimulus, the other to be associated with chronic infection in some distant organ or with some chronic intoxication. The data available were insufficient to justify an opinion as to a possible effect of this change upon the function of the hypophysis.—J. P. S.

Influence of hypophyseal extracts, of acetyl-choline and of histamin on the coronary arteries of the tortoise (O vlivu hypofysy, acetylcholinu a histaminu na koronární arterie želvi). Sumbal (J.), Brat. Lek. Listy, 1925, **4**, 94-98. (Summary in French.)

Under the influence of hypophyseal extracts the coronary arteries of the tortoise undergo dilatation. The reaction appears when the substance is applied to the coronaries by injection into the heart beating at its normal rhythm or when it is transfused in Ringer's solution through the vessels. If atropin is administered to the tortoise the vasodilatation caused by hypophyseal extract is diminished only to a slight extent. The blood pressure always falls even if the ventricular rhythm remains normal. The ventricular contraction is slightly diminished.—R. G. H.

A case of carcinoma of the hypophysis (Ein Fall von Hypophysiskarzinom). Takaizumi (M.), Tr. Jap. Path. Soc. (Tokyo), 1923, **13**, 229-232.

A man 46 years old for 6 years had suffered from bitemporal hemianopsia. Death resulted suddenly from hemorrhage from an ulcer of the stomach. At the site of the hypophysis was a mass

1.8 x 2 x 1.5 cm. which pressed upon the pons, the tuber cinereum and the corpora mamillaria. The tumor was composed of small cells whose cytoplasm was either nongranular or finely granular and stained faintly with basophilic dyes. There were occasional isolated large multinucleated cells. In the anterior portion of the anterior lobe a transition could be made out between chief cells and tumor cells. Numerous areas of necrosis were observed in the tumor mass, and many small, thin-walled blood vessels were occluded with a fibrin-like mass. The author concluded that this neoplasm was a carcinoma originating in the chief cells of the anterior lobe of the hypophysis.—J. P. S.

Pituitrin hyperglycaemia and the antagonism between pituitrin and insulin. Voegtlin (C.), Thompson (J. W.) & Dunn (E. R.), J. Pharmacol. & Exper. Therap. (Balt.), 1925, **25**, 137.

Pituitrin injected subcutaneously into albino rats, starved 18 hours, in doses corresponding to 140 mg. of fresh posterior lobe per kilogram body weight, produced a rise in blood sugar lasting a few hours. When given intravenously to female rabbits in doses corresponding to 0.7 to 7 mg. fresh posterior lobe per kilogram body weight a similar hyperglycemia was produced. Indications were obtained that the toxicity of insulin in rats is decreased by a simultaneous subcutaneous injection of pituitrin.—G. E. B.

Exper'mental variations in the action of pituitary extract (Uber die Beeinflussbarkeit der Hypophysenhinterlappenextrakte). Zondek (H.) & Bernhardt (H.), Ztschr. f. klin. Med. (Berl.), 1925, **101**, 312-319.

Zondek had previously observed that the effect of thyroid extract could be modified by calcium, potassium, and pH, and he now reports the effect of calcium and potassium on the action of pituitary extract in restraining diuresis and promoting a concentration of the urine. For this purpose he made use of two patients with **diabetes insipidus.** The urine was collected in hourly specimens for a period of 7 hours on a series of days. On the first day no treatment was given and the degree of polyuria defined. On the second day 2 ampoules of pituitrin ("physormon") were given intravenously; this effected a marked decrease in the quantity and increase in the concentration of the urine. When the extract was mixed with 100 mg. KCl in the syringe and immediately injected the action of the pituitrin was intensified, whereas when 150 mg. $CaCl_2$ was substituted the action of the pituitrin was almost annulled. When the $CaCl_2$ was injected into one arm and the pituitrin into the other a normal pituitary effect was obtained. Confirmation of these observations was obtained by similar experiments on the diuresis of the Volhard water test in normal persons, and by similar tests applied to dogs. It was further observed that

when the injections of calcium and pituitrin were repeated the restraining action of the calcium progressively diminished and might change to an augmenting action; however, if the injections were discontinued for three weeks the original restraining action was restored. When injected separately from the pituitrin the calcium had no effect unless very large amounts were employed. The authors conclude that potassium and calcium act by altering the colloidal state of the hormone to one more nearly approaching that in which it normally enters the cells, and that the body has in this mechanism the power of modifying the action of pituitrin on the cells to suit their passing needs.—Med. Sc. **12**, 271.

Internal secretions [Beitraege zur Pathologie der inneren Sekretion (VI Mitteilung)]. Nakamura (H.), Tr. Jap. Path. Soc. (Tokyo), 1923, **13**, 135-138.

A study of 8 cases of struma nodosa convinced the author that this condition does not develop in a normal thyroid gland from post-fetal conditions, but on the basis of a developmental anomaly of the thyroid. It is often associated with anomalies of other organs. In 41 cases of acute tuberculosis, Nakamura found the thyroid involved in only one case and that by extension from adjacent structures. Miliary tubercles are frequent in the thyroid in acute miliary tuberculosis. In most cases of tuberculosis there is more or less increase of interstitial tissue in the **thyroid.** In 2 cases of dementia precox, the author found the normal proportion of cortex and medulla of the **adrenals** disturbed with relatively smaller mass of medulla; the thyroid was definitely of the colloid type.—J. P. S.

Diabetes in pregnant woman and in fetus (Diabète grave chez une femme enciente et diabète de congenitale chez l'enfant, considerations sur des lésiones définitives secondaries à une acidose transitoire). Ambard, Merklen, Schmid & Arnovlgevitch, Bull. et mém. Soc. méd. d. hôp. (Par.), 1925, **49**, 547-555.

A woman, aged 35, with grave diabetes, gave birth (eighth month) to an infant with diabetes (12 gm. of sugar per liter of urine). The mother died in a few hours, the child after 23 hours. Necropsy showed lesions in the maternal and in the fetal pancreas. Evidently the diabetes developed in the woman because the pancreas deficiency was not compensated by the affected fetal pancreas. The fatal outcome, after hyperglycemia had disappeared under insulin treatment, is ascribed by Ambard and his co-workers to lesions of the liver and kidneys, caused by transient acidosis.
—J. Am. M. Ass., **84**, 1785.

The respiratory exchange after insulin injection and sugar ingestion (Uber den respiratorischen Stoffwechsel nach Insulin-Applikation und Zuckerzufuhr). Bornstein (A.) & Holm (K.), Ztschr. f. d. ges. exper. Med. (Berl.), 1924, **43**, 376-390.

These experiments were carried out in normal and diabetic men and in depancreatectomized dogs, the object being to ascertain whether insulin hypoglycemia is associated with increased carbohydrate combustion. The authors conclude that neither in normal nor diabetic patients can hypoglycemia be accounted for by increased carbohydrate oxidation. A small increase in carbohydrate oxidation may indeed be seen in some instances after the conclusion of the blood sugar fall, but the increase is too small and occurs too late to be regarded as the cause of the hypoglycemia. Under insulin treatment both human diabetics and depancreatized dogs recover the capacity to burn levulose as well as dextrose.

—Med. Sc., **11**, 451.

Evidence of regeneration of the Pancreas in an insulin treated case of diabetes. Boyd (Gladys L.) & Robinson (W. L.), Am. J. Pathol. (Bost.), 1925, **1**, 135-146. 1 plate.

Report of a case of a 9 year old boy who had had diabetes since the age of 2. A suitable Allen diet had been strictly adhered to. In 1922, insulin treatment was begun. At that time he weighed 30 pounds, was 39 inches in height, and was more or less drowsy and unhappy. He was unable to utilize even 15 grams of carbohydrate. Along with the insulin he was given a diet adequate for a boy of his age. In a year his tolerance to carbohydrate had trebled, as shown either by the fact that 30 units of insulin controlled the disease as well as had 90 a year before, or without insulin he could metabolize 45 grams of carbohydrate instead of 15. From a chronic invalid in 1922 he became the leader of the "gang" in 1923. He was killed by fracturing his skull. The pancreas was removed 30 minutes after death. It presented no gross abnormalities. Microscopically, the number and size of the islet cells gave no indication of the existence of diabetes. The only abnormality was an occasional pyknotic nucleus in some of the islet cells. Many evidences of regeneration of the acinar, centro-acinar and islet cells were observed. While there had been a marked rise in sugar tolerance, it had never reached normal. The rise in sugar tolerance would indicate either that the islets were not irreparably injured, or if so, that regeneration had taken place to compensate for the loss.—J. P. S.

The insulin problem (Das Insulinproblem). Brugsch (T.) & Horsters (H.), Klin. Wchnschr. (Berl.), 1925, **4**, 436-438.

The metabolism of glucose goes through the following stages. Glycogen (diastase) — glucose (glucolysis) — lactic acid, O_2 and H_3PO_4 (phosphatesis) — *d*-fructose diphosphoric acid, CO_2 and H_2O (di- and poly-saccharesis) — intermediate polysaccharides that give principally *d*-fructose on hydrolysis — glycogen. In the absence of insulin this process is interrupted at the glucolysis stage. Depancreatized animals can convert fructose into glycogen (polysac-

charesis) and also possess an active phosphatase. Insulin is the thermostable coenzyme of phosphatesis, i. e., it is necessary for the conversion of lactic acid into *d*-fructose diphosphoric acid. Experiments are given to prove this contention. The relationship of insulin to fat metabolism is discussed.—Chem. Abst., **19**, 2073.

Congenital pancreatic disease with infantilism. Clarke (C.) & Hadfield (G.), Quart. J. Med. (Oxford), 1924, **17**, 358-364. 2 plates.

Report of the case of a girl 4 years, 4 months old, who had suffered from a fatty diarrhea certainly from the 5th month, and probably from birth. Facial expression and weight was that of a child of 2 years; height that of a child of 3. The abdomen was distended, due in part to enlargement of the liver. The urine was normal. The stools averaged 5 per day, were unformed, voluminous, pale, and fat droplets were visible to the naked eye and microscopically. There were no fatty acid crystals. Death resulted from bronchopneumonia following nasal diphtheria. At postmortem examination there was found at the site of the pancreas a mass of fat in which was a thin strand of gland tissue, estimated as one-twentieth of the normal total, and containing what appeared to be an excessive amount of islet tissue. The pancreas was undergoing slow replacement fibrosis; although there was no clear evidence of pancreatitis. The liver showed marked fatty metamorphosis unaccompanied by necrosis. A chronic colitis was present with ulcers in the descending colon only.—J. P. S.

Insulin and liver glycogen. Cori (C. F.), J. Pharmacol. & Exper. Therap. (Balt.), 1925, **25**, 1-33.

Starving rabbits show no appreciable change in their liver glycogen in the first hour of insulin action whether the initial glycogen content is high or low, or whether the fall in blood sugar is slight or strong. In the period from the second to the sixth hour of insulin action the liver glycogen may remain constant or may decrease. Starving mice behave similarly. Insulin produces glycogen synthesis whenever there is a certain excess of sugar available. The excess of sugar need not necessarily be derived from administration from without, since the excess production of sugar in the body itself as it occurs during phlorhizin poisoning and after complete pancreatectomy leads to glycogen synthesis when insulin is injected.—G. E. B.

High blood sugar with absence of sugar in urine. Major (R. H.) & Davis (R. C.), J. Am. M. Ass. (Chicago), 1925, **84**, 1798.

Major and Davis have seen several patients who showed high values for blood sugar but nevertheless had no sugar in the urine. On several occasions an attempt was made to lover the blood sugar by increasing the dose of insulin, with the result that they had a

mild insulin shock. In treating these patients, the high blood sugar values have been ignored and the diet and dosage of insulin have been based entirely on the urinary findings. Such management has proved satisfactory, although several of the patients worry when their blood sugar is elevated, though they have no sugar in the urine. Two explanations of this condition are suggested. It is possible that in these patients there was an abnormally high renal threshold, this term being used in its present accepted sense. Another possibility is that through the action of the insulin the normal blood sugar is changed into some other substance not readily excreted, but which gives the same copper value as blood sugar. The practical lesson learned from the study of these patients is that the estimations of the urinary sugar have been a safer guide to therapy in this group of patients than the blood sugar determinations.

—A. M. A.

The effect on the blood sugar of fish of various conditions, including removal of the principal islets. McCormick (N. A.), & Macleod J. J. R.), Proc. Roy. Soc. (Lond.), 1925, **98 B**, 1-29.

Intramuscular injection of adrenalin caused marked hyperglycemia, reaching its maximum in about 2 hours. Insulin similarly given had only a slight effect on the blood sugar. Removal of the islets was followed by marked hyperglycemia.—G. E. B.

Insulin: its intradermal injection. Müller (E. F.) & Corbitt (H. B), J. Lab. & Clin. Med. (St. Louis), 1925, **10**, 695-703.

The authors report the results of an experimental study. The effect of insulin varies with the route of administration. The effect of insulin injections upon the blood sugar content of normal rabbits is markedly increased if the intradermal method of administration is employed; subcutaneous injections of the same amount of insulin into the same as well as into different animals are less effective. A comparison of intradermal, subcutaneous, and intravenous injections of equal amounts of insulin shows that their effectiveness decreases in the order mentioned. The degree and the period of effectiveness does not depend upon the rapidity of resorption, but upon a hitherto unknown factor, very probably related to the action of the involuntary nervous system. This property seems to be inherent in the skin rather than in the subcutaneous tissues or in the body fluids.—R. G. H.

Acute diabetes following mumps. Patrick (A.), Brit. M. J. (Lond.), 1924, **ii**, 802.

Pancreatitis is a relatively common complication of mumps, but glycosuria and diabetes appear to be very rare. Patrick describes a case of diabetes commencing a fortnight after the onset of mumps in a girl aged 8. Death resulted in coma in a few weeks. The author has been able to find only 2 other cases of definite

diabetes following mumps in the literature. In none of these 3 cases was there any abdominal pain such as occurs in pancreatitis.—Med. Sc., **11**, 333.

Case of caeliac disease with glycosuria. Poynton (J. F.), Proc. Roy. Soc. Med. (Lond.), 1925, **18**, 38-39 (Sec. Dis. Child.).

The patient was a male child of 7, with extreme abdominal distension and general wasting. A year before there had occurred an attack of severe diarrhea, the present illness having gradually developed since that time. Glycosuria (6%) was present with a blood sugar concentration of 0.44%; no acetone was present. Stools contained 48.2% of fat. Dietary and **insulin** treatment yielded considerable improvement.—I. B.

A symptom complex in diabetes that may be confused with the reaction of insulin overdosage. Smith (B.), Calif. & West. Med. (San Fran.), 1925, **23**, 311-313.

Diabetic patients who are extremely undernourished may suffer with periods of muscular weakness, pallor, sweating, and other symptoms which may be confused with those of insulin overdosage. The one is due to hyperglycemia, the other to hypoglycemia.—I. B.

Studies of the carbohydrate metabolism of infants. Tisdall (F. F.), Drake (T. D. H.) & Brown (A.), J. Lab. & Clin. M. (St. Louis), 1925, **10**, 704-711.

A preliminary communication on the inference drawn from 500-600 blood sugar determinations in infants. The procedure was based on the Shaffer-Hartman method, with the use of only 0.2 cc. of blood. In apparently normal infants the average concentration of blood sugar was found to be 0.087%. In the presence of marasmus the percentage was from 0.070 to 0.050. Attention is directed to the tremendous ability of the normal infant to utilize glucose introduced parenterally. Infants with conditions such as acute intestinal intoxication and fermentative diarrhea are unable to utilize glucose with the same rapidity as normal infants. The authors are making a study of the effect of **insulin** in these cases.—I. B.

Transplantation of the pancreas (Studien ueber die Transplantation des Pankreas). Ukai (S.), Tr. Jap. Path. Soc. (Tokyo), 1923, **13**, 156-157.

Ukai transplanted the pancreas of rabbits into the spleen. The animals were killed at intervals varying from 15 minutes to 817 days after the operation. Auto- and homoio-transplants usually grew, while hetero-transplants degenerated and disappeared. The acinous elements in the transplanted tissue were very sensitive to abnormal influences; while the islands of Langerhans were much

more resistant. Regenerated islands were found in good condition 800 days after the transplant had been made.—J. P. S.

Diabetes refractory to insulin. Umber (F.) & Rosenberg (M.), Klin. Wchnschr. (Berl.), 1925, **4**, 583-588.

Umber and Rosenberg found all of their 13 patients with harmless glycosuria to be refractory to insulin. Another group of 10 refractory patients had high blood sugar or considerable glycosuria, but their disturbances were comparatively benign. The glycosuria is relatively independent of the glycemia in these cases. The authors do not regard them as true pancreatic diabetes.

—J. Am. M. Ass., **84**, 1607.

Antagonistic action of glycerol on insulin intoxication. Voegtlin (C.), Dunn (E. R.) & Thompson (J. W.), J. Pharmacol. & Exper. Therap. (Balt.), 1925, **25**, 168.

The coma and convulsions supervening in albino rats starved for 18 hours and injected with a M.L.D. of insulin subcutaneously are promptly removed by intraperitoneal injection of about 1 g. per kilogram body weight of a 20% solution of pure glycerol. The same result is obtained by a slow intravenous injection of the same amount of glycerol. Among a large number of substances tested only glucose and glycerol were found to be efficient antidotes.

—G. E. B.

The pathology of diabetes, with special reference to pancreatic regeneration. Warren (S.) & Root (H. F.), Am. J. Pathol. (Bost.), 1925, **i**, 415-429. 1 plate.

The pathologic changes in 26 cases of diabetes are presented. The duration in 8 of these is known to have been over 14 years. Thirteen cases showed hyalinization of the islands of Langerhans. Only one of these patients was under 45 years of age. Five cases showed varying degrees of sclerosis of the islands. In three others there was slight lymphocytic infiltration about scattered islands; and the islands in five appeared normal, though decreased in number in two of these five. Apparently normal islands were present in all pancreases examined, no matter how badly damaged the bulk of the islands may have been. In two subjects, treated with insulin for over 5 months, there seemed to be more islands of normal appearance than in those under dietary treatment. The character of the lesions in the islands of Langerhans suggested a toxic origin, and an injurious agent acting over a long period of time. The increased fibrous tissue found in certain pancreases in diabetes is due to destruction of island or acinar cells or both, with persistence and condensation of their stroma. The parenchymal tissue regenerates and forms new stroma, with resulting increase of connective

tissue. The acinar tissue of the pancreas does not show evidence of increased fibrosis in cases of diabetes of short duration. Insulin treatment decreases the frequency with which glycogen is found in the nuclei of liver cells and in the epithelium of Henle's loops. The frequency of severe myocardial damage due to coronary sclerosis, is high in diabetics over 40 years of age. The patients who developed gangrene averaged 44 per cent overweight, while the others averaged 26 per cent overweight. On the basis of these studies a new interpretation is offered of the pathology of the pancreas in diabetes mellitus. The long-continued action of an injurious agent (or possibly excessive functional activity) causes gradual destruction of island, and at times of acinar, cells. New cells are formed to take their place, only to be exposed to the same injurious influence with consequent pathologic change. Their injury is followed by production of still more new cells. Eventually the destructive process wears down the regenerative powers of the pancreas, thus explaining the unfavorable course of the disease. In pneumonia and other infectious diseases, the pancreas readily regenerates after acute injury. The disturbed carbohydrate metabolism giving rise to abnormal fat and protein metabolites may be the cause of the high incidence of vascular disease in diabetic patients.—J. P. S.

Xanthosis of hands and feet in diabetes mellitus ("Ochrodermatosis" of Castellani, "Xanthochromia Cutis" of French authors). Weber (E. P.), Proc. Roy. Soc. (Lond.), 1924, **18,** 18 (Sec. Dermoid).

In a man of 20 in the hospital for treatment of diabetes mellitus, insulin yielded relief from glycosuria and hyperglycemia. He was readmitted 4 months later with a canary-yellow discoloration of the skin confined especially to the palms of the hands and soles of the feet. The blood plasma had a milky yellow appearance which could be clarified by shaking with ether. The ether likewise extracted the pigment. The taking by the patient of large quantities of green vegetables, especially cabbage and carrots, containing the pigment carotin, was regarded as probably having an important bearing on the development of the xanthosis.—I. B.

The hypertrophy of the submaxillary gland in the albino rat, following parathyroidectomy. Appleton (J. L.), Am. J. Pathol., 1925, **1,** 217-223.

That the submaxillary glands of rats hypertrophy after parathyroid extirpation was reported by Hammett. Microscopic study of the glands of 7 animals showed that the hypertrophy is at least largely attributable to an increased volume of the individual parenchyma cells. This was the only difference distinguishable between the submaxillaries of the parathyroidectomized animals and those of thyro-parathyroidectomized or of control animals. Specifically, there was no histological evidence of any hyperemic, fibrotic, in-

flammatory, proliferative, degenerative or infiltrative process. A search of the literature has failed to reveal any other instance of submaxillary hypertrophy associated with a disturbance of parathyroid function.—R. G. H.

On the transplantation of the parathyroid in homologous animals. Kurokawa (K.), Tr. Jap. Path. Soc. (Tokyo), 1923, **13**, 153-154.

In 100 rats the author made 25 successful transplants of parathyroid tissue. In the experimental rats, the majority showed atrophy of the **thymus, pancreas** (especially the islands of Langerhans), **generative glands** and **hypophysis.** The **thyroid** gland was usually atrophied. The **adrenals,** especially the cortex, and the **pineal** gland showed various changes but no atrophy. The bones were generally atrophied, the epiphyseal lines were narrowed and the arrangement of the cartilage cells irregular; but there was no increase in the cartilage cells as seen in rickets. The changes in the other organs were irregular and not specific.—J. P. S.

Further experiments on the removal of the pineal body in the chicken. Izawa (Y.), Tr. Jap. Path. Soc. (Tokyo), 1923, **13**, 144-153.

One hundred and five chickens were employed in this study, 80 being subjected to pinealectomy and 25 used as controls. Copious details are reported in the cases of 11 fowls. As a result of these experiments the author concludes that pinealectomy in the chicken yields positive results; that pinealectomized cocks show earlier development of the comb and testes, grow more rapidly, crow prematurely and give earlier evidence of sexual instinct than do normal controls; that pinealectomized hens reveal premature development of the **ovaries** and oviducts and lay eggs earlier than the controls. Therefore, in the case of pinealectomized chickens sexual maturity is reached earlier than in controls.—J. P. S.

The function of the spleen. Hall (H. A.) & Ablahadian (E.), Calif. & West. Med. (San Fran.), 1925, **23**, 289-294.

A survey of the current views on the function of the spleen with an account of the authors' work in this field. In rabbits receiving splenic extracts intravenously there was a marked increase in blood calcium, reaching its greatest height 24 hours after the injection. In 12 to 14 hours the blood calcium again reached normal. Addition of a small amount of parathyroid substance to the splenic substance served to retard the elimination of the excess calcium from the blood. It is therefore concluded that the spleen is a stimulant to calcium metabolism, preparing suitable calcium salts for the blood stream and body cells. In view of these findings it is suggested that splenic and **parathyroid** extract may be of value in treatment of pulmonary tuberculosis.—I. B.

A study of thymus glands. Bliss (G. L.), Arch. Pediat. (N. Y.), 1925, **42**, 213-226.

Out of 1400 new-born, there were 70 cases of what the author considered dangerously enlarged thymus glands, which is about 5%. The ages ranged from one hour to eight months. Forty-five were in boys and 25 in girls. Of 68 subjects treated, 4 have died. The others were at the time of the last report well and entirely free from symptoms. To the symptoms of dyspnea, coughing and choking, stridor and cyanosis, the author adds two more: an unusual amount of gas distention in the bowels and stomach. He has found that after the second or third treatment with x-rays, there is an improvement in this condition. Another symptom noted was that a baby with an enlarged thymus holds its head extended backward between the shoulders in an effort to ease its respiration and by thus opening more freely the upper aperture of the chest removes the pressure on the trachea. All apparently so-called enlarged thymus glands do not have symptoms and are not considered dangerous when they are symptom free. The norm for the thymus gland for a baby of a given size, age and weight has not been established. Bliss advocates the term "symptom producing thymus" in preference to "enlarged thymus." X-ray treatment is efficient and unattended with danger.—M. B. G.

Status lymphaticus, interim report of the committee appointed jointly with the Medical Research Council. J. Path. & Bacteriol. (Edin.), 1925, **28**, 132.

This interim report is based upon a study of 236 cases, of which 20 were subjects 15 years or over in whom an entirely glandular thymus was present, and 216 cases of sudden death in apparently healthy persons of any age. Of the latter, 144 were due to gross trauma, 12 were associated with anesthesia, 6 with convulsions, 7 were unexplained, and 1 was a doubtful case of thymic asphyxia; for the remainder an efficient cause of death was found. With the understanding that the number of cases is too small to warrant definite conclusions, the committee puts forward the following tentative statements: (1) The normal thymus, as observed in persons dying of accident, shows considerable variation in weight even in subjects of the same age. The average hospital patient dying from disease of some duration does not represent the normal healthy condition. (2) In the few cases recorded in which the cause of death was not discovered, the proportion with a large thymus was not greater than might be explained by chance. The same is true of anesthetic deaths. (3) In this series, therefore, **there is no evidence to show that there is any connection between the presence of a large glandular thymus and death from unexplained or trivial causes.** (4) Thymic asphyxia would appear to be a condition of rare occurrence, depending upon some unrecog-

nized anatomical relationships and only in part referable to the size of the thymus. (5) The association of deaths from convulsions with the presence of a glandular thymus appears to be in the nature of a natural association, since deaths from this cause occur during early infant life when the presence of a glandular thymus is to be expected. (6) The occasional association of a glandular thymus with evidence of feminism, as described by various authors, is confirmed. (7) The association of an enlarged and persistent and glandular thymus with **Graves' disease** is fully established.

—J. P. S.

Thymic syphilis (Ueber Syphilis der Thymusdruese). Fujii (S.), Tr. Jap. Path. Soc. (Tokyo), 1923, **13**, 158-159.

Brief reports of 4 cases of syphilis of the thymus in children ranging from 1 month to 9 years old. Syphilitic changes in the thymus include gummas, chronic interstitial inflammation, syphilitic arteritis and phlebitis, proliferation of the reticulum and epithelium, and infiltration with numerous "histiocytes" and plasma cells. Nonspecific but frequently observed are, sclerosis and lymphocytic infiltration of Hassall's corpuscles with diminution of the eosinophile cells.—J. P. S.

Enlarged thymus; differential diagnosis and radium treatment. Grier (G. W.), Atlantic M. J. (Harrisb.), 1925, **28**, 502-506.

A decided enlargement of the thymus exists in a considerable percentage of new-born babies. While there is often no associated symptomatology, in a few instances this condition will cause serious trouble or even prove fatal. All cases should be considered as potentially serious, and therefore placed under treatment. Quoting Pfahler, the author mentions the direct symptoms of thymus enlargement as follows: "Inability to cry loudly, crowing respirations when crying, noisy respirations during sleep, difficulty in nursing, twitching, fretfulness and other nervous symptoms, vomiting, regurgitation, feeble respiration, grunting as though the child wants to have a stool, slow or retarded development, failure of the child to gain in weight in spite of proper dietary measures, inanition, obesity, cough and hiccough." In children past the age of 2 there may be an acquired disorder of the chest which occasionally is confused with enlarged thymus. Congenital syphilis and enlargement of the great vessels are most apt to be confused with enlarged thymus. The diagnosis depends upon an increase in the size of the mediastinal shadow and not upon a displacement of it. Treatment consists of the use of x-ray or radium. With radium the response is more prompt and application easier and safer.—I. B.

Iodin treatment of goiter. Bircher (E.), Klin. Wchnschr. (Berl.), 1925, **4**, 742-745.

Bircher attributes the increase of the incidence of toxic goiter

to the iodin treatment of goiters. There are over 3,500 cases of exophthalmic goiter in Switzerland. Subjects of adenomatous goiter are frequently injured by iodin. Over 2,000 instances of this have been reported in Switzerland. He considers small doses given for a long period more dangerous than single large doses. Hypertonia and hyperperistalsis of the stomach with hyperacidity is one of the symptoms of the injury. **Diabetes** is aggravated by iodin. Sterility in the second and third generation was observed experimentally. The author advises caution with iodin and combination with phosphates, calcium, quinin, silicates, or substitution of these remedies for it.—J. Am. M. Ass., **84**, 1881.

The juvenile thyroid. Blankmeyer (H. C.), Illinois M. J. (Oak Park), 1925, **47**, 55-62.

Thyroid hyperfunction is rare in children, while hypofunction is common. Malnutrition is in most instances a condition of "athyrosis," which usually implicates other glands as well and is characterized by overweight at birth, and late dentition, walking and talking. Judicious thyroid opotherapy is the outstanding treatment.

—I. B.

Some quantitative relationships of thyroxin calculated from its calorigenic action. Boothby (W. M.) & Baldes (E. J.), J. Pharmacol. & Exper. Therap. (Balt.), 1925, **25**, 139.

A critical study of the rate of decay of the excess heat production following the injection of thyroxin in 2 myxedematous patients verifies the logarithmic form of decay previously suggested by Boothby and Sandiford. Knowing the rate of loss per day from the decay curve and combining it with the experimental value, the concentration of thyroxin in a particular patient was found to lie between 5 and 8 mg. for the maintenance of a normal metabolic rate.—G. E. B.

Susceptibility of thyroidectomized animals towards certain toxins. Busso (R. R.), Compt. rend. Soc. de biol. (Par.), 1925, **92**, 820-821.

The great sensitivity of thyroidectomized animals towards **insulin** is corroborated. **Adrenalin** (phenol also) is toxic in the same dose to both normal and operated rats. The effect of morphine is more irregular but seems somewhat more toxic for the thyroidectomized rat. Results obtained with KCN are paradoxical. Thus, normal rats are more sensitive to this than thyroidectomized, the symptoms of poisoning appearing sooner and in a more severe form; the lethal dose also is smaller. On the contrary, thyroidectomized rabbits are the more sensitive and the lethal dose for them is 15 mg. per kg., whereas for the normal animal it is 25 mg.

—Chem. Abst., **19**, 2242.

The thyroid during pregnancy. Daly (P. A.) & Strouse (S.), J. Am. M. Ass. (Chicago), 1925, **84**, 1798-1800.

Observations on 25 cases have led to the belief that pregnancy, by increasing the need for thyroid activity, makes excessive demands upon that gland, diminishes the store of iodin contained therein, and unless the intake of iodin is sufficiently increased may produce a state of functional or physiologic overstrain of the thyroid which presents a clinical picture of hyperthyroidism. Administration of iodin will relieve this syndrome. The possibility exists that this functional disturbance may be a basis for the very common nervous instability of the pregnant woman, and for some of the toxemias of pregnancy.—R. G. H.

The influence of circulatory disturbances on the gaseous exchange of the blood. V. The blood gases and circulation rate in hyperthyroidism. Davies (H. W.), Meakins (J.) & Sands (J.), Heart (Lond.), 1924, **11**, 299-308.

As hyperthyroidism is the only condition, other than the physiological state of the body under exercise, in which there is an increased metabolism and an overacting circulatory system, the changes which occur in the gaseous exchange of the blood and the general circulation rate have been estimated in cases of exophthalmic goiter. The oxyhemoglobin and carbon dioxide dissociation curves are found to be approximately normal; while the partial pressure of carbon dioxide in the alveolar air is uniformly higher during periods of active hyperthyroidism than during periods when the thyroid function is normal. There is a close relation between the minute volume output of the heart and the increase of metabolism. After thyroidectomy the systolic output of the heart decreases.—Med. Sc., **12**, 101.

The effect of thyroid extract and of thyroxin upon the response to adrenaline. Dryerre (H.), Quart. J. Exper. Physiol. (Lond.), 1924, **14**, 221-224.

In 4 cats to which thyroid "extract" was administered a diminution of the pressor reaction to adrenalin was obtained during periods up to 66 minutes. Thyroxin gave ambiguous results in 8 cats and 2 rabbits. These experiments fail to corroborate the theory that thyroid sensitizes the sympathetic nervous system.

R. G. H.

Mucin deposits in myxedema. Dufour (H.), Hurez & Pau, Bull. Soc. méd. d. hôp. (Par.), 1925, **49**, 780.

Dufour, Hurez and Pau affirm that the edematous effusion accompanying myxedema contains mucin which may accumulate in the tissues, and form deposits similar to the tophi in gout. In a woman, aged 62, the mucin deposits developed on the tips of two

fingers, causing pains wrongly attributed to chronic rheumatism. Puncture of the edema revealed the presence of mucin. Under thyroid treatment the tophi, as well as the pains in the fingers and the headache, disappeared.—J. Am. M. Ass., **85**, 308.

Auricular fibrillation in thyro-toxic conditions. Dunhill (T. P.), Fraser (F. R.) & Scott (A. W.), Quart. J. Med. (Oxford), 1924, **17**, 326-338. 1 plate.

The authors present reports of 15 cases of auricular fibrillation associated with exophthalmic goiter. In 4 patients the fibrillation was transitory; in the other 11 it was persistent. In the latter group, in 2 cases there was little evidence of general thyrotoxicosis; in 3, a return to normal sinus rhythm occurred after partial thyroidectomy; in 4, a return was brought about by quinidine after partial thyroidectomy; in 1, quinidine produced a stable sinus rhythm following improvement in the thyrotoxic condition without operative treatment; and in 1, there was no improvement under medical treatment and the results of quinidine were transient. Electrocardiographic tracings from two patients are given. The authors conclude that thyrotoxic auricular fibrillation is associated with an active toxic cause; that removal of the cause, as by partial thyroidectomy, will result in a return to a stable sinus rhythm in a proportion of cases; and that quinidine will bring about a return to a stable sinus rhythm, if the cause has been removed and the auricular fibrillation persists.—J. P. S.

Goiter in infants (Zur Behandlung des Kropfes in Säugling). Eckstein (A.), Arch. f. Kinderh. (Stuttg.), 1925, **76**, 7-13.

Wieland does not confirm the relative resistance of infants to iodin. He and Hamburger urge caution in dosage and duration of iodin treatment. Eckstein usually observed dyspeptic stools and failure to gain on the application of iodin ointment. As soon as the reduced goiter ceases to menace suffocation, he discontinues the iodin treatment. He recommends treatment of goiter in infants by small doses of iodin, in spite of possible iodin injury, as sure and rapid reduction of large goiters follows, and no other practical treatment is at present available. It requires regular oversight by the physician.—J. Am. M. Ass., **84**, 2031.

Goiter prophylaxis in Switzerland (Kropfprophylaxe in der Schweiz). Eggenberger (H.), München. med. Wchnschr., 1924, **71**, 972-977.

The examination of school children showed that after the first year of taking iodin the thyroid glands diminished in size. This was noted in children entering the first grade. Prophylaxis must begin in the preschool age. The effect of properly exercised prophylaxis shows best in the new born. Some women use iodized salt, some do not. None of the offspring of the users of iodized salt showed

palpable increase of the thyroid gland, while 50% of the others did as in former years. Five-tenths gram of potassium iodid to 100 gm. sodium chlorid is sufficient.—Am. J. Dis. Child., **29**, 851.

Changes in the blood, especially in the blood sugar concentration after exposure of the thyroid gland to x-rays. Fogelberg (H.), Acta med. Scand. (Stockholm), 1924, Suppl. **7**, 68-73.

Fogelberg studied the effects on the blood sugar curve of radiating the thyroid gland. Twenty-two subjects were studied, comprising 3 having exophthalmic goiter, 13 "thyroid intoxication," and 4 simple goiter. Two subjects were normal. The x-ray dosage was 1⅜ "unit skin doses" (H. E. D.) to each lobe or 1/10 H. E. D. to one lobe. The blood sugar curves of the subjects were determined both without sugar and after 100 gm. glucose. No effect of the radiation was observed in the former case, but after sugar administration in the thyroid cases usually a change in the curve was seen. With the larger thyroid doses a distinct depression of the sugar curve followed, hence the effect on the thyroid was regarded as destructive. With the 1/10 H. E. D. doses the curves approached the hyperthyroidism type, hence the effect of the radiation was apparently stimulating.

Data on coagulation time and blood cell counts were also included.—R. G. H.

Goiter heart. Foster (N. B.), Am. J. M. Sc. (Phila.), 1925, **169**, 662-668.

The author gives the following summary of the salient points of his paper. Cardiac symptoms associated with thyroid disease are of common, even usual occurrence, but these symptoms may be of pronounced severity without detectable evidence of heart disease. The so-called cardiac deaths which follow operation are seldom due to heart failure but more often to vascular failure; that is to say, there is, in these cases, a vasomotor paralysis and a widening of the peripheral vascular field notable by a sharp drop in the diastolic blood pressure, a condition similar to shock. The commonest type of disorder referable to the heart in thyrotoxicosis is auricular fibrillation. Whether this arrhythmia is due to lesions in the myocardium or to nervous influences is not yet known. Lesions in the myocardium have been described in cases of thyroid disease and they have been experimentally induced in animals, but these lesions are not found in every case. Heart block and auricular flutter are of exceptional occurrence and probably denote serious myocardial degeneration. It is important to control auricular fibrillation, especially if operation be contemplated, since the mortality in cases with fibrillation is higher than in controlled cases. A reversion to normal rhythm may be usually secured by proper treatment, which includes rest, digitalis and quinidin.—R. G. H.

Iodine in exophthalmic goitre. Fraser (F. R.), Brit. M. J. (Lond.), 1925, **i**, 1.

Fraser gives the results of his investigations into the therapeutic effect of iodin in cases of exophthalmic goiter as carried on over a period of several years. Throughout he used a 10% tincture, the iodin being dissolved in 95% alcohol without potassium iodide. Since March, 1921, 24 cases have been investigated. Full details of a series of these cases are given, together with charts showing the pulse rate, body weight and basal metabolic rate. In general there was a very marked improvement as shown in a diminution of the heart rate and the basal metabolic rate, and a striking improvement of the general condition. Fraser points out, however, that this improvement was not maintained, and that if the patient went home there was usually a relapse which was not relieved by further administrations of iodin, although the patient might feel better. In five of the cases there was no beneficial action, possibly because three of them had coincident infection. In two cases, in which larger doses had been given, the symptoms were quite distinctly aggravated, and Fraser points out that doses of 9-15 drops daily give as good results as could be obtained with larger doses. If such doses, however, were long continued the thyroid gland would become gradually harder and the symptoms would again become more marked, but if the dose be reduced to 3-6 drops daily it could be continued almost indefinitely. He shows also that this drug simply gives a relief and not a cure, for if the administration be stopped the condition immediately relapses, and any worry, excitement, or infection may undo all the benefit derived from the iodin. (These results are in entire agreement with those which had been obtained at the London Hospital, where it is customary to treat every patient with this disease with a course of Lugol's iodin before operation. The dose of this has to be very carefully regulated and must not be continued for too long. As a form of preoperative treatment it appears to be of extreme value, but as a means of bringing about a cure it is apparently useless.) Fraser points out that it is difficult to decide on the meaning of this action of iodin, for although it is tempting to try to bring exophthalmic goiter into line with the simpler goiters as an iodin deficiency disease, the results of iodin treatment merely justify the view that there is an iodin deficiency relative to the needs of the body.—Med. Sc., **12**, 229.

Thyroid regression in different diseases [Beziehungen der regressiven Veraenderungen der Schilddruesen zu den verschiedenen Krankheiten (II Mitteiling)]. Fukushi (M.) & Eguchi (K.), Tr. Jap. Path. Soc. (Tokyo), 1923, **13**, 138-140.

This report is based upon a study of the thyroid glands from 286 subjects, and is concerned especially with the relation of lipoid

content of the gland to various diseases. The authors conclude that the lipoid substance in the glandular epithelium is directly related to the associated disease. In cases of ulcer of the stomach, uremia, pyemia, septicemia and the nephritis of pregnancy there was an increase in the lipoid content. In this group of cases the presence of lipoids is intimately related to changes in the condition of the blood. The increased lipoid content of the thyroid in cases of carcinoma, sarcoma and pulmonary tuberculosis depends upon the cachexia associated with these diseases. In arteriosclerosis the increase in lipoids is due to circulatory disturbances in the gland. The marked increase in lipoids in exophthalmic goiters is a result of the hyperfunction of the thyroid. In the fetus, in the newborn and in small children there is only a very slight increase in lipoid content of the thyroid.—J. P. S.

Goiter incidence in school girls of New York City. Goldberger (I. H.) & Aldinger (A. K.), Am. J. Dis. Child. (Chicago), 1925, **29**, 780-798.

This present survey was undertaken primarily for the purpose of determining the extent, type and degree of thyroid involvement in a cosmopolitan group of girls of school age residing in known nongoitrous district. In the latter respect, the present survey differs from the previous studies by other investigators who surveyed districts of known endemic origin. If an incidence were established, the results could be used for the recommendation of prophylactic and curative measures. The 11,084 children observed were selected at random from 7 schools, and one miscellaneous group (graduates of high schools from Manhattan and The Bronx, private schools and out of town high schools). For the purpose of classification they may be grouped as follows: (a) children attending elementary schools and (b) high schools; (c) young women entering the junior year of the New York Training School for Teachers. The study disclosed that enlarged thyroids were most prevalent between the ages of 13 and 15 years. The greatest incidence of thyroid enlargement was in the slightly enlarged group, 17.2%; moderately enlarged, 2.6%; markedly enlarged, 0.5%; total, 20.3%. Thyroid enlargement in colored children was approximately 7% less frequent than in the white children. Some observers state that a racial immunity to endemic goiter exists. Although the study suggests that the percentage of incidence of normal glands seems to vary inversely with the activity of the menstrual cycle, the findings should not be construed as conclusive. A distinct relationship exists between thyroid incidence and such signs as tremor, mottling and exophthalmos. Girls whose mothers were of foreign birth showed the least incidence of thyroid enlargement.

—R. G. H.

The treatment of goiter in infants (Ueber Kropfbehandlung bein Säugling). Hamburger (F.), München med. Wchnschr., 1924, **71**, 1815.

A newborn infant with a large goiter received 0.001 gm. of sodium iodide once daily for 8 days. On the eighth day the goiter had disappeared and medication was stopped. The child was on the breast but the weight dropped, the stools became slimy and the child died in 3 days. Another infant of 8 months of age had a large goiter making a retropharyngeal tumor. Under medication with sodium iodide, a total of 0.3 mg., and a thyroid preparation, a total of 15 mg., the goiter disappeared in a week.

—Abst. Am. J. Dis. Child.

Studies on the thyroid apparatus. XXII. The growth of the reproductive system of male and female albino rats following thyro-parathyroidectomy and parathyroidectomy at seventy-five days of age. Hammett (F. S.), Am. J. Anat. (Phila.), 1924, **34**, 195-214.

Hammett shows that age, sex, stage of development, and nutritive condition of the animals are important factors in the determination of the degree of response of the reproductive system to the growth inhibiting effects of thyroid-parathyroid deficiency, and the toxemia of parathyroid deprivation. Age is a factor in that the younger rats have the greater absolute growth curve and the greater resistance to the retardative effects of glandular deprivation. Sex is a factor in that the males are less sensitive than the females to thyroid-parathyroid deficiency, and there appears to be a sex-specific degree of susceptibility in the males to the toxemia following parathyroid removal at 75 days of age. The relation of age to sex differences in gonad dependency and relation to thyroid function were found to be correlatable with the sex relation of goiter incidence to age. This supports the previously stated hypothesis that one of the main factors in the greater incidence of thyroid disturbances (particularly goiter) in women is that there exists a greater inherent constitutional relation between ovary and thyroid function than between that of thyroid and testis.

—Abstracted from author's summary.

Studies on the thyroid apparatus. XXIV. The growth of the heart, lungs, liver, kidneys, spleen, submaxillary glands, and eyeballs in the albino rat thyro-parathyoidectomized and parathyroidectomized at 75 days of age. Hammett (F. S.), Am. J. Anat. (Phila.), 1925, **35**, 223-238.

The growth of the heart, lungs, kidneys, spleen, submaxillary glands, liver in the males, and eyeballs in the females was less retarded by thyroid (thypar) deficiency initiated at 75 days of age than by a like procedure at 100 days. The sex differences in re-

sponse were in general quantitatively less in the younger than in the older group. This can hardly be due to sex differences in normal growth capacity as such, for the change in these on age would indicate a greater instead of a lesser divergency. It is, therefore, probably due in large part to sex-specific differences in stage of physiological development as related to the modifying influences of the gonadal incretions. The differences in the growth response of these organs to thyroid (thypar) deficiency from that of the body weight were less in the younger than in the older group. That is to say, the quantitative values tended to cluster more closely around that of the body as a whole. This may be an expression of a decreasing intensity of common type activity with advancing age in the sense of a greater differentiation in specific growth and functional characteristics. There was evident a tendency for the growth of the various organs to be more retarded by the toxemia of parathyroid deficiency initiated at 75 days of age than by the same condition initiated at 100 days. In the males the lungs and submaxillary glands were exceptions, in the females the submaxillary glands and the eyeballs. This greater retardation in the younger animals is to be attributed to a cumulative effect of the toxemia, due either to its longer duration, its greater intensity, or both. The possible participation of the stage of development is a factor which should not be neglected.

—Abstract from author's summary.

The relation of dysmenorrhea to interstitial thyrotoxicosis as proved by therapeutic measures. Hertzler (A. E.), Am. J. Obst. & Gynec. (St. Louis), 1925, **9**, 783-797.

On a basis of extensive personal experience Hertzler concludes that many young women present small goiters associated with mild degrees of thyrotoxicosis. Anatomically these glands show changes in the colloid, inactive acinal epithelium and apparently an increase in the cells situated between the acini. Many of these patients have an associated dysmenorrhea without demonstrable anatomic changes in the pelvic organs. When these patients are treated in the conventional manner for their goiters the dysmenorrhea disappears in the vast proportion of cases. This applies as well to the common groin pains so commonly diagnosed chronic appendicitis, for the relief of which appendectomy is wholly impotent.—R. G. H.

Standardization of thyroid preparations. Hunt (R.), Arch. Int. Med. (Chicago), 1925, **35**, 671-686.

Hunt reviews some of the more important literature and concludes from that and from recent data from his own laboratory that the physiologic activity of thyroid preparations as determined by the acetonitril test on mice and by clinical observations closely parallels the iodin content. Little or no physiologically inactive iodin

was found by his tests in the thyroids of adult animals. Very small amounts of non-thyroid iodin in adulterated thyroid preparations could be detected by the acetonitril test and also by simple chemical tests. Very few of the thyroid preparations on the market comply with the U. S. P. standard; they were found to vary greatly in physiologic and therapeutic activity.—R. G. H.

Standardization of thyroid. Hunt (R.), J. Pharmacol. & Exper. Therap. (Balt.), 1925, **25**, 138-139.

Commercial preparations of thyroid were found to affect the resistance of mice to acetonitril, the basal metabolism in myxedema and the clinical condition in a case of cretinism in direct proportion to the iodin content of the product. No "inactive" iodin was found in the preparations. It is believed that thyroid preparations should be standardized by their iodin content. Sheep thyreoglobulin administered by mouth to mice protected the animals against acetonitril to the same degree as did entire gland with the same amount of iodin; injected intravenously the thyreoglobulin had no effect upon the resistance. Thyrotoxin given intravenously was slightly less active than thyreoglobulin (containing the same amount of iodin) given by mouth.—G. E. B.

Studies on amphibian metamorphosis. II. Huxley (J. S.), Proc. Roy. Soc. (Lond.), 1925, **98 B**, 113-145.

The effects of various substances on metamorphosis were studied. Iodin and thyroid were found to act quantitatively. Estimations of the rate of change were made by measuring the length of body, tail and limbs at definite intervals.—G. E. B.

Goiter in children. Jackson (A. S.), Arch. Pediat. (N. Y.), 1925, **42**, 363-374.

Iodine deficiency is generally accepted as the cause of simple or colloid goiter in children. Excessive physical and mental fatigue are also factors in the etiology of simple goiter, as they add an extra load to the thyroid gland. Goiter in children may be classified into colloid, adenomatous and exophthalmic types. The adenomatous type is subdivided into three classes: non-toxic, toxic, and iodine hyperthyroidism. Colloid and adenomatous goiters are the result of a compensatory hypertrophy of the thyroid gland to supply the deficiency of thyroxin. Although the colloid goiters apparently produce no symptoms the disturbance in the thyroid may result in a general impairment of the vitality of the body. Adenomatous goiters rarely become toxic in children except by the injudicious use of iodine. Exophthalmic goiter rarely occurs in children under 10 years of age; it is observed more frequently between 20 and 40. Nine children with exophthalmic goiter, all but one of whom received treatment with iodine, were successfully

operated upon. All children living in the goitrous district should receive prophylactic treatment with iodine, and this should be started at the age of 10 years. If small adenomas are present treatment may be continued until the age of 21, provided small doses are given with care.—M. B. G.

The origin of adenomatous goiter. Kline (B. S.), Am. J. Pathol. (Bost.), 1925, **1**, 235-239. 2 plates.

From a study of over six hundred adenomatous goiters, Kline found no evidence that this condition depends upon a development after puberty of embryonic thyroid cell rests. On the other hand, this material indicated that adenomatous goiter arises from adult thyroid tissue, and that it depends essentially upon an irregularity in the degree of proliferation of acini in different portions of the gland.—J. P. S.

Four cases of exophthalmic goiter treated with insulin. Lawrence (R. D.), Brit. M. J. (Lond.), 1925, **i**, 753.

The author states that the idea of treating hyperthyroidism with insulin was founded on the hypothesis of an antagonism between the hormones of the thyroid and the **pancreas.** Such an hypothesis admits of no definite proof, but the evidence strongly warrants such a deduction. The author shows that experimental work on animals is definitely in support of a thyroid-insulin antagonism. Care was taken in investigating his patients to watch them in bed, to allow the preliminary improvement due to rest to come to an end before starting the insulin treatment. Observations were taken on the weight, the pulse rate, the basal metabolic rate, and the respiratory quotient. Full details of four severe cases of Graves' disease are given, together with the doses of insulin, which varied from 20-100 units. The insulin was well borne and caused no inconvenience. Two cases were greatly improved, one being practically normal on discharge from hospital. The two others were not essentially benefited, although one gained much in weight and felt better.—Med. Sc., **12**, 230.

Use of borax in hyperthyroidism. Loeper (M.) & Ollivier (J.), Bull. Soc. méd. d. hôp. (Par.), 1925, **49**, 734-737.

Sodium borate was successfully used by Loeper and Ollivier in 6 patients with hyperthyroidism. Under the influence of the drug the cardiac as well as nervous and digestive disturbances improved; the size of the thyroid gland was reduced and the exophthalmos ameliorated. The sodium borate was given in a daily dose of from 2 to 4 gm. of a 5% solution. A similar solution of sodium citrate may be added. The drug was taken with meals, or exceptionally was introduced by the rectum. The efficacy of borax is ascribed to its selective action on the thyroid.—J. Am. M. Ass., **85**, 308.

Pathology of myxedema (Contribution à l'étude des lésions du myxœdème congénital l'idiotie myxœdémateuse de Bourneville). Marinesco (M. G.), Encephale (Par.), 1924, **10**, 265-291.

A detailed study of the nervous system and other organs in a case of myxedematous idiocy in a girl of 15 years. There was a congenital absence of the thyroid and the usual signs of athyroidea. At 13 years of age a piece of thyroid was grafted into the abdominal wall. This was followed by a general improvement both mentally and physically for 6 weeks, after which the graft atrophied and the symptoms retrogressed. The patient died 2 years later of general tuberculosis. Microscopic study of the entire nervous system was made and as a control the brain of a normal child of the same age was used. Changes of arrested development were found, both the cerebrum and the cerebellum being involved. There was retardation of the cellular development of all the cortical layers with a diminution in the volume of all the layers. There was also a decrease in the volume of the cells of the basal nuclei but no evidence of changes in the cellular structure. The cells of Cajal persisted in the hippocampus and other areas. Outside of the nervous system all the tissues showed a reduced volume of parenchyma, but some had large vesicular nuclei containing globules and were decreased in chromatin content.—Abst. Am. J. Dis. Child.

The treatment of obesity. Mason (E. H.), Canad. M. Ass. J. (Toronto), 1924, **14**, 1052-1056.

In this paper the author describes a method of treating certain cases of exogenous obesity by a combination of a subcaloric diet and the use of thyroid extract. It is claimed that the results are uniformly satisfactory, and the cases described support this contention. These are chiefly of the type developing after child birth and associated with menstrual disorders, especially amenorrhea. The treatment is based upon a subcaloric diet in an attempt to lower the nitrogenous exchange. No attempt is made to maintain nitrogenous equilibrium. The use of thyroid extract is controlled by repeated estimations of the basal metabolic rate which the author attempts to maintain at a level of about plus 10%. The uncontrolled employment of thyroid extract is strongly condemned. The metabolic investigations of three patients are reported in detail over periods of several months. Summarized, the following conclusions were arrived at: There is a direct relation between intake of protein and urinary nitrogenous loss; with the greater intake of calories per day the tissue nitrogen loss is less. But it appears that the total calorie intake is not the determining factor in the rate of rapidity of loss of weight, but that the original weight of the individual plays a part. The greater the initial weight, the more rapidly can a reduction be accomplished. Also it was found that in the subjects showing the greatest loss of

weight less body protein was consumed per unit loss of weight. This would be expected, as the greater the initial obesity the greater the percentage of the total weight would be due to fat.—Med. Sc., **11**, 352.

Riedel's struma associated with remnants of the post-branchial body. Meeker (L. H.), Am. J. Pathol. (Bost.), 1925, **1**, 57-68. 6 plates.

Meeker reports a case of Riedel's "iron-hard struma" in a man 50 years old. A gradually increasing, painless enlargement of the thyroid gland had been observed for 4 or 5 months. No symptoms of either hypo- or hyper-thyroidism were mentioned. The tonsils were enlarged and there was a severe inflammation of the pharynx and trachea. The thyroid was removed and measured 19 x 6 x 4 cm. Riedel's struma is a chronic inflammation of the thyroid and presents clinical manifestations of malignant disease of this organ. This patient, as is usually the case, recovered upon removal of the thyroid. Total extirpation is frequently followed by myxedema. Anatomically, the disease is characterized in its early stages by hyperplasia of the thyroid parenchyma, and later by infiltration with lymphocytes, plasma cells and eosinophilic leucocytes. Later, as a sequence to degeneration of the parenchyma, fibrosis occurs and may become very marked. The adjacent lymph glands show chronic inflammation. A specific etiologic agent has not been recognized. In Meeker's case there were regenerative activity on the part of the parenchyma and persistent cell nests and accessory cysts representing the post-branchial body. Meeker considers the possibility that an inflammation of the pharynx and trachea may extend to the thyroid by way of the post-branchial system. Twenty-five cases of Riedel's struma and eleven observations of post-branchial bodies in human subjects, collected from the literature, are briefly summarized.—J. P. S.

The nose, throat and larynx in thyroid disease. Nebinger (R.), Atlantic M. J. (Harrisb.), 1925, **28**, 573-578.

The author believes that focal infections of the upper respiratory tract, especially of the tonsils and teeth, apparently bear a causal relationship in the production of thyroid enlargements, especially when associated with hyperthyroidism. The larynx should be examined before and after thyroidectomy in order to determine the margin of safety in thyroid operations. Care should be taken not to traumatize the trachea and larynx during the operation.—L. B.

Transitory congestive thyroid enlargement. Orgel (S. Z.), Am. J. Dis. Child. (Chicago), 1925, **29**, 41-50.

The author describes a transient tumor mass appearing in the neck which he thinks is a congestion of the superficial and perhaps the deeper blood vessels of and about the thyroid gland. It may

be either unilateral or bilateral. Because it was found in the thyroid region and because in two of his five subjects there was a continuous mass across the entire front of the neck, as if both lateral lobes and isthmus were involved, the author calls the condition "transitory congestive thyroid enlargement." Forced respiration, as in crying, boisterous laughter, shouting, singing and blowing of wind instruments, brings on the tumor mass, which disappears on the resumption of normal respiration.—M. B. G.

Electrical treatment of exophthalmic goiter (Sur le traitement électrique du goitre exophthalmique). Portret (S.) & Helie (Y.), J. de radiol. et d'électrol. (Par.), **9**, 55-56.

This disease has been variously treated because of the diversity of its symptoms. The authors review these treatments briefly: (a) Surgery: unsatisfactory and now, at least in France, completely abandoned; (b) Medical: drugs, chiefly iodin; organotherapy, a long treatment but results often good; use of thyroid to be condemned by reason of the risk of aggravation, but **ovarian** opotherapy often useful; (c) Electrical treatment: faradization, according to Charcot, requires only time to effect a cure; the general condition improves, the patient sleeps better, irritability diminishes, the tumor decreases, and the pulse slows. With the continuous current one of the first effects is lessening of the swelling and rapid improvement of the general condition: the appetite improves, weight increases, and the vasomotor and menstrual troubles pass off; the pulse is also quickly slowed down. Galvano-faradization has also yielded cures. In no case is electrical treatment contra-indicated, and there is no reason to fear shock, hemorrhage, infection, or **myxedema**, and, locally, no disfigurement, no "fine linear cicatrix," as the surgeons describe it, no radio-dermatitis, and no telangiectases. The galvanic current should be of 60-110 volts applied through spongy electrodes soaked in warm water, 10 by 7 cm. negative and 20 by 15 cm. positive, the latter placed between the two shoulders, 15 ma. for 20 minutes, 3 sittings weekly. and, after 20 sittings, one month's rest. The whole treatment may last 8-10 months; any desquamation or vesication is easily controlled. Details are given of 20 cases; in 97% the tumor diminished; in 75.8% the pulse slowed; the trembling was reduced in 81.2%, and the exophthalmia in 45.2%.

Today radiotherapy has supplanted mere electrical methods, but cases are known in which these have given good results where radiation has failed. Belot, at the Seventeenth International Medical Congress, London, 1913, summarized the effect of radiation as soothing to the irritable nervous condition, return of the faculty of sleep, disappearance of the sense of fatigue, improvement of the general condition, and quieting of the cardiac troubles, the pulse gradually coming down to normal. The action on the goiter itself

is much less rapid and only begins when these other improvements have been effected, while the exophthalmia often resist the x-rays. Details are also given of 10 cases in which radiation was of no avail, but which yielded more or less permanently to current electricity. The authors conclude that in view of the results of cases cited the use of the galvanic current in this disease has been too much neglected, and especially in view of the 10 cases in which x-rays failed to yield any good results. It may, however, be useful to combine the two methods. The great point in favor of the simple current is its harmlessness in whatever way it may be used, and it has a double effect in regulating the disturbance of function of the thyroid and other glandular secretions, and in acting as a sedative to the sympathetic nervous system. It deserves at least to be fairly tried.—Med. Sc., **12**, 258.

The thyroid influence on the behavior of the white rat. Rickey (Edna), Comp. Psychol. Monogr. (Balt.), 1925, **2**, S. N. 12. Williams & Wilkins Co., Baltimore.

A somewhat elaborate study was made of the effects of thyroid conditions on the learning ability of rats tested in a maze. Among other results the following are reported. The lethal dose for animals over 50 days old was 0.6-0.8 gm. daily. Large doses produced languor, inactivity or hyperactivity, increased respiration, increased pulse and difficulties of locomotion. Thyroidectomy caused progressive incoordination of behavior. Movements became slower, less stable and meaningless. The skill acquired in the maze before operation was lost. Progressive deterioration in vitality and the vegetative processes ensued. The effects were more pronounced in younger animals. In males sex activity disappeared, but the females did not become sterile. The administration of thyroid substance caused hyperactivity with loss of skill and accuracy in behavior with many random movements and increase in number of errors. Normal males mated with thyroidectomized females produced small offspring that showed locomotor and vasomotor deficiencies. Under thyroid treatment their learning, behavior condition and general vitality rapidly approached normal, though there was little increase in size. The offspring of thyroid fed males and females appeared normal but had little ability to learn in the maze. The second generation offspring of normal males and thyroidectomized females but with normal sires were small and had motor deficiencies. Their learning ability improved markedly under thyroid treatment but they remained much under sized.—R. G. H.